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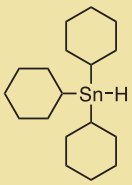
VOL. 35, NO. 3 • 2002
(Last issue in 2002)

Applications of Ionic Liquids in Organic Synthesis

Novel Methods of Resolving Racemic Diols and Amino Alcohols

New PRODUCTS

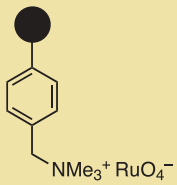
46,068-0 Tricyclohexyltin hydride, 97%



Utilized in the hydrostannation of a variety of functionalized alkenes in good yields.

Jousseaume, B. et al. *Organometallics* **1995**, *14*, 685.

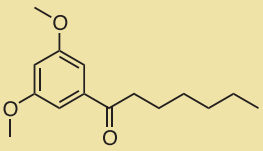
51,158-7 Perruthenate, polymer-bound



Has been used in the oxidation of pyridylcarbinols,[1] hydroxylamines,[2] benzylic alcohols,[3] and primary alcohols to their corresponding aldehydes.

(1) Habermann, J. et al. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253. (2) Hinzen, B.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1. (3) Haunert, F. et al. *ibid.* **1998**, 2235.

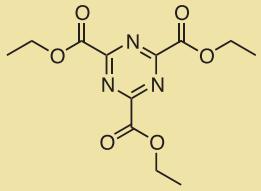
57,553-4 1-(3,5-Dimethoxyphenyl)heptan-1-one, 96%



An intermediate in the synthesis of functionalized cannabinoids.[1,2]

(1) Papahatjis, D. P. et al. *J. Med. Chem.* **1998,** *41,* 1195. (2) Harrington, P. E. et al. *J. Org. Chem.* **2000,** *65,* 6576.

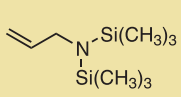
57,669-7 Triethyl 1,3,5-triazine-2,4,6-tricarboxylate, 97%



A reactive azadiene that is very useful in inverse-electron-demand Diels–Alder reactions for the efficient synthesis of highly functionalized pyrimidines.[1] Also utilized in the synthesis of purines and purine analogs via Diels–Alder reactions with aromatic dienophiles.[2]

(1) Dang, Q. et al. *J. Org. Chem.* **1996**, *61,* 5204. (2) Dang, Q. et al. *J. Am. Chem. Soc.* **1999,** *121,* 5833.

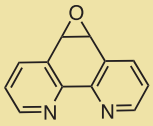
57,893-2 2-Allyl-1,1,1,3,3,3-hexamethyldisilazane, 97%



Was utilized to generate aminoalkylboronic acids.

Goeller, B. et al. *Main Group Metal Chemistry* **1997**, *20*, 795.

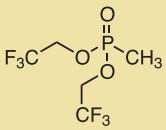
57,878-9 5,6-Epoxy-5,6-dihydro[1,10]phenanthroline, 98%



Versatile reagent that has been employed in syntheses of 5-substituted 1,10-phenanthrolines[1] and in the preparation of the marine alkaloid ascididemin.[2]

(1) Riklin, M. et al. *J. Chem. Soc., Dalton Trans.* **2001**, 1813. (2) Moody, C. J. et al. *Tetrahedron* **1992,** *48,* 3589.

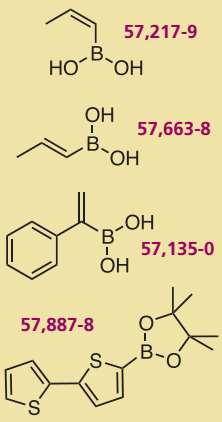
57,944-0 Bis(trifluoroethyl) methylphosphonate, 99%



An excellent starting material for the stereoselective synthesis of Z α,β-unsaturated esters[1] and ketones.[2]

(1) Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (2) Yu, Y. et al. *ibid.* **1999**, *40*, 6725.

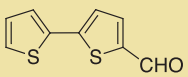
57,217-9 *cis*-Propenylboronic acid
57,663-8 *trans*-Propenylboronic acid
57,135-0 α-Phenylvinylboronic acid
57,887-8 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2′-bithiophene



Vinyl boronic acids, like arylboronic acids, undergo facile Suzuki–Miyaura coupling with aromatic halides in the presence of palladium catalysts.[1] Several years ago, Miyaura and coworkers demonstrated the utility of cyclic pinacol esters of arylboronic acids in Suzuki–Miyaura coupling reactions.[2,3] Very recently, α-phenylvinylboronic acid was used for the preparation of the corresponding nonracemic alcohols via asymmetric hydrogenation, in the presence of a chiral rhodium catalyst, followed by oxidative cleavage.[4]

(1) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (2) Ishiyama, T. et al. *J. Org. Chem.* **1995**, *60*, 7508. (3) Ishiyama, T. et al. *Tetrahedron Lett.* **1997**, *38*, 3447. (4) Ueda, U. et al. *J. Organomet. Chem.* **2002**, *642*, 145.

57,670-0 2,2′-Bithiophene-5-carbaldehyde, 98%



Useful in medicinal chemistry[1,2] and materials science.[3,4]

(1) Rodriguez, M. J. et al. *J. Antibiot.* **1998**, *51,* 560. (2) Xu, W.-C. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9,* 2279. (3) Kamal, M. R. et al. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *126,* 65. (4) Soudan, P. et al. *J. Mater. Chem.* **2001,** *11,* 773.

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About Our Cover

Cattleya Orchid and Three Brazilian Hummingbirds (oil on wood panel, 34.8 x 45.6 cm), signed and dated 1871, was painted by the American artist Martin Johnson Heade. Heade's earliest works were portraits, but by the early 1860s he had turned to landscape, a subject more attuned to his artistic personality. Using a limited number of pictorial elements: sky, clouds, water, perhaps some trees or rocks in an essentially flat landscape, Heade created an art of varied and shifting moods. Often his portrayal of natural phenomena such as shifting sunlight, approaching rain, lightning, dark clouds, and fog gives his paintings a dramatic and even disquieting character.

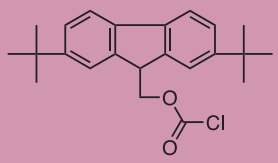
Photograph © Board of Trustees, National Gallery of Art, Washington.

During the 1860s, Heade turned to painting objects at close range, and produced a series of remarkably sensuous still life paintings of flowers. In 1863, he sailed to Rio de Janeiro to study and paint the major species of tropical hummingbirds for a book. The book was never published, but he made two other trips to Central and South America in 1866 and 1870, fascinated by the wildlife and the landscape. His approach was different from that of his friend Frederick Edwin Church, who also traveled to Latin America, but who sought to capture the grandeur of vast tropical landscapes, and it was different from that of naturalists like John James Audubon, whose purpose was to create an objective record of the birds and plants he saw. In *Cattleya Orchid and Three Brazilian Hummingbirds*, Heade carefully represents a specific kind of pink orchid and two particular species of hummingbird, one Sappho Comet, green with a yellow throat and red tail feathers, and two green-and-pink Brazilian Amethysts, but he sets these subjects in an evocative and mysterious tropical setting full of mist and diffuse light, combining the two kinds of painting at which he excelled, still life and landscape.

This painting is a gift of the Morris and Gwendolyn Cafritz Foundation to the National Gallery of Art, Washington, DC.

"Please Bother Us."

Clint Lane, President



Professor James S. Nowick of the University of California, Irvine, kindly suggested that we offer the amine-protecting group 2,7-di-(*tert*-butyl)-9-fluorenylmethyl chloroformate (Fmoc*-Cl) as an alternative to Fmoc-Cl. Dr. Nowick and coworkers have demonstrated that Fmoc*-protected amines have a greater solubility in common volatile organic solvents and fewer problems associated with byproduct removal than their Fmoc-protected counterparts.

Stigers, K. D.; Koutroulis, M. R.; Chung, D. M.; Nowick, J. S. *J. Org. Chem.* **2000**, *65*, 3858.

55,100-7
2,7-Di-(*tert*-butyl)-9-fluorenylmethyl chloroformate, 97% (Fmoc*-Cl)

Naturally, we made this valuable protecting group. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

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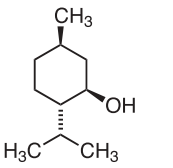
Lab Notes

(1*R*,2*S*,5*R*)-(–)-Menthol: Proposed Calibration Standard for Polarimetry

Since its discovery in the early part of the nineteenth century,[1] polarimetry has been employed extensively in the sugar[2] and pharmaceutical industries,[3] and for the analysis of chiral compounds[4] and asymmetric synthesis products[5] and catalysts.[6] Polarimetry is also used in the teaching laboratory.[7,8]

While glucose and sucrose solutions are the most commonly utilized international standards for calibrating polarimeters,[9] their use suffers from the following disadvantages:



(1*R*,2*S*,5*R*)-(–)-Menthol

- Their solutions can become easily contaminated with bacteria or fungi.
- Sucrose can hydrolyze to a mixture of glucose and fructose, with a resulting reversal of the optical rotation.[10]
- Mutarotation is observed for solutions of glucose, which give constant rotations only after some hours.[11]

Thus, we thought it desirable to search for a new polarimetry standard, which ought to be stable, inexpensive, and easy to prepare and purify. We conducted preliminary tests on several candidates [(+)-tartaric acid, quinine sulfate, ephedrine, and *l*-menthol] and compared the results with those obtained with glucose and sucrose:

- Aqueous solutions of (+)-tartaric acid[12] and quinine sulfate racemized slowly and did not give stable readings.
- Aqueous solutions of ephedrine hydrochloride[13] (generated in situ from the free base and hydrochloric acid) gave stable readings, but, after three months, these readings changed due to racemization.

In contrast, we obtained good results with (1*R*,2*S*,5*R*)-(–)-menthol,[14] which may be obtained by resolving racemic synthetic menthol,[8] by asymmetric synthesis,[15] or, more commonly, from the essential oils of several species of mint, e.g., *Mentha piperita* or *Mentha herbensis*.[16] It is also commercially available,[17] inexpensive (much less so than ephedrine or quinine sulfate), and easy to purify by recrystallization or sublimation[14]—even easier than sucrose or glucose. We found ethanolic solutions of (–)-menthol to be stable for years.

We used samples of enantiomerically pure natural (–)-menthol[18] of constant melting point (41–42 °C), and checked their chemical purity by the method of Ligor and Buszewski.[19,20] The purities obtained fell in the range of >99.9 to 100%. We then measured the absolute optical rotation of a 10% solution of (–)-menthol in absolute ethanol on a JASCO DIP 370 digital polarimeter. 27 measurements were carried out at 25 °C over a period of 72 days. The average of these measurements, $[\alpha]_D^{25}$ = -50.40 ± 0.01 (c = 10, C_2H_5OH), compares very favorably with the reported value of $[\alpha]_D^{25}$ = -50 (c = 10, C_2H_5OH).[8,14,17]

We have been routinely using such an ethanolic solution of natural menthol (stored in a tightly closed vial) as a polarimeter calibration standard for over three years. We have obtained very stable readings during this period, and found no evidence of decomposition or loss by evaporation.

References and Notes

(1) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994; pp 2–3. (b) The first practical polarimeter was constructed in 1840. Biot, J. B. *Ann. Chim. Phys.* **1840**, *74*, 401; http://museum.nist.gov/panels/bates/intro.htm (accessed May 14, 2002). (2) Ulber, R.; Faurie, R.; Sosnitza, P.; Fischer, L.; Stärk, E.; Arbeck, C.; Scheper, T. *J. Chromatogr., A* **2000**, *882*, 329. (3) Maier, N. M.; Pilar, F.; Lindner, W. *J. Chromatogr., A* **2001**, *906*, 3. (4) Goodall, D. M. *Trac-Trend Anal. Chem.* **1993**, *12*, 177; *Chem. Abstr.* **1993**, *119*, 155032m. (5) Huerta, F. F.; Minidis, A. B. E; Backvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 221. (6) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (7) Mosher, M. D.; Kelly, C. O.; Mosher, M. W. *J. Chem. Educ.* **1996**, *73*, 567. (8) Poiré, C.; Rabiller, C.; Chon, C.; Hudhomme, P. *J. Chem. Educ.* **1996**, *73*, 93. (9) National Institute of Standards and Technology (NIST). *Standard Reference Materials*; SRM No. 17e and 917b. http//www.srmcatalog.nist.gov/srmcatalog/tables/204-6.htm (accessed May 8, 2002). (10) Eggleston, G.; Vercelotti, J. R. *J. Carbohydr. Chem.* **2000**, *19*, 1305. (11) Yamabe, S.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 4519. (12) Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. *J. Chem. Soc.* **1959**, 2492. (13) Goss, C. A.; Wilson, D. C.; Welser, W. E. *Anal. Chem.* **1994**, *66*, 3093. (14) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, U.K., 1988; p 215. (15) Milone, C.; Gangemi, C.; Neri, G.; Pistone, A.; Galvagno, S. *Appl. Catal. A, Gen.* **2000**, *199*, 239. (16) Veronese, P.; Li, X.; Niu, X. M.; Weller, S. C.; Bressan, R. A.; Hasegawa, P. M. *Plant Cell. Tiss. Organ Cult.* **2001**, *64*, 133. (17) For example, Aldrich Chemical Company. *Handbook of Fine Chemicals and Laboratory Equipment,* U.S. ed.; Milwaukee, WI, 2003–2004; p 1161, cat. no. M278-0. Also available at www.sigma-aldrich.com. (18) Brazilian standard pharmaceutical grade, which is equivalent to USP grade. The samples were obtained from Drogasil or Henrifarma). (19) Ligor, M.; Buszewski, B. *J. Chromatogr., A* **1999**, *847*, 161. (20) HP 5890 II gas chromatograph; HP5, cross-linked 5% methyl silicone capillary glass column (30 m x 0.32 mm x 0.25 μm); nitrogen carrier gas; the injector temperature (200 °C), the FID temperature (250 °C), and the heating program were the same as those reported by Ligor and Buszewski.

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Applications of Ionic Liquids in Organic Synthesis†

*Hua Zhao and Sanjay V. Malhotra**
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New Jersey Institute of Technology
University Heights
Newark, NJ 07102, USA
E-mail: malhotra@njit.edu

Outline

1. Introduction

An ionic liquid (IL) is a liquid consisting of ions only, but this definition is different from the classic definition of a molten salt.[1] The latter is a high-melting, highly viscous, and highly corrosive liquid, while an ionic liquid is liquid at a much lower temperature (< 100 °C) and has a lower viscosity. Currently, a major drive is underway in industry and academia to substitute more environmentally friendly technologies for traditional ones in which damaging and volatile organic solvents are heavily used. Ionic liquids are considered as environmentally friendly substitutes for volatile organic solvents, not only because of their low vapor pressures, but, more importantly, also because of their ability to act as catalysts. Moreover, ionic liquids possess several other attractive properties, including chemical and thermal stability, nonflammability, high ionic conductivity, and a wide electrochemical potential window.

Ambient-temperature, alkylpyridinium (RPy^+) chloroaluminate based ionic liquids were first reported in the early 1950s.[2] However, the report by Wilkes and co-workers[3a] of 1,3-dialkylimidazolium-based chloroaluminate ionic liquids, that possess favorable physical and electrochemical properties, provided the impetus for a dramatic increase in activity in this area.[3b] Ionic liquids usually consist of inorganic anions and nitrogen-containing organic cations, and their chemical and physical properties can be finely tuned for a range of applications by varying the cations or anions.[4] For example, varying the anion X in [EMIM][X] changes the melting point of the ionic liquid in the range of –14 to 87 °C.[5] The fact that they can now be produced with melting points at or below room temperature (as low as –96 °C) has been an important reason why ionic liquids have been explored in many applications.[1]

Recent reviews have surveyed the behavior of halogenoaluminate(III) ionic liquids in many reactions including dimerization, polymerization, and multiphase hydrogenation.[5,6] Since halogenoaluminate(III)-type ionic liquids are sensitive to moisture, their applications in chemical reactions have been limited. Stable, room-temperature ionic liquids (RTILs) have been studied in many chemical processes, for example, bio-processing operations,[7] as electrolytes in electrochemistry,[8,9] in gas separations such as the capturing of CO_2,[10] in liquid–liquid extractions,[11,12] and as heat-transfer fluids.[13] However, since most studies have employed ionic liquids as green solvents or catalysts for organic synthesis, this review will summarize recent research on the applications of RTILs in organic reactions.

2. Composition of Ionic Liquids

The most commonly used cations in room-temperature ionic liquids are alkylammonium, alkylphosphonium, *N*,*N*′-dialkylimidazolium ([RR′IM]), and *N*-alkylpyridinium ([RPy]) cations (**Figure 1**).[5] The most commonly utilized alkyl chains are methyl, ethyl, butyl, hexyl, octyl, and decyl. The most commonly investigated IL anions are shown in **Table 1**.[4,14-22]

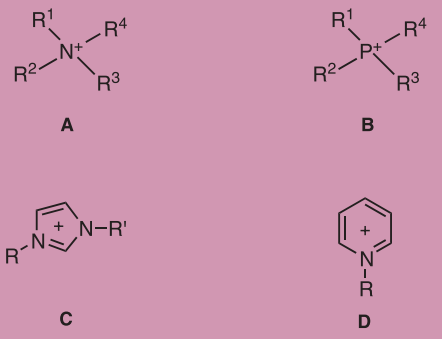
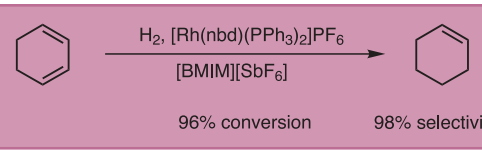


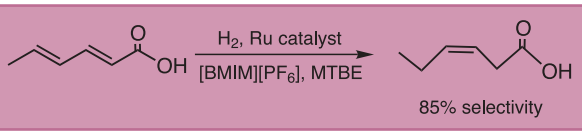
Figure 1. Important Cation Types in Room-Temperature Ionic Liquids.

Table 1. Examples of Anions Commonly Found in Ionic Liquids

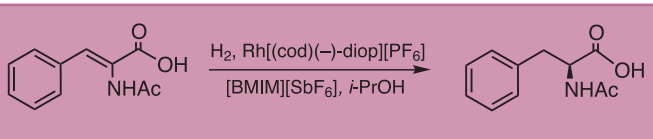
Anion	Reference	Anion	Reference
BF_4^-	4	$(CF_3SO_2)_2N^-$	17
PF_6^-	14	$CF_3CO_2^-$	17
SbF_6^-	15	$HexBEt_3^-$	18
$CH_3CO_2^-$	4	OTs^-	19
HSO_4^-	16	$AuCl_4^-$	20
NO_3^-	4	$AlCl_4^-$	21
NO_2^-	4	Carborane anions	22
$CF_3SO_3^-$	17		



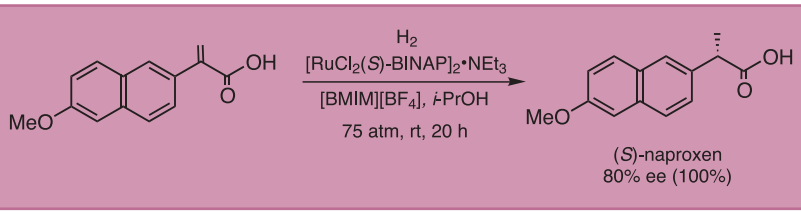
eq 1



eq 2



eq 3



eq 4

3. Transition-Metal-Mediated Catalyses

3.1. Hydrogenation

Ionic liquids can dissolve organometallic compounds and provide a polar, weakly coordinating medium for transition-metal catalysts. In this case, ionic liquids are used as inert solvents or co-catalysts.

The [Rh(nbd)(PPh_3)$_2$][PF_6] (nbd = norbornadiene) catalyzed biphasic hydrogenation of 1-pentene in ionic liquids [BMIM][PF_6] (BMIM = 1-*n*-butyl-3-methylimidazolium) and [BMIM][SbF_6] was first reported in 1995 by Chauvin and co-workers.[23] The reaction rate in the IL was five times higher than the one obtained by using acetone as solvent. Furthermore, the catalyst solution in the ionic liquid was reused without significant loss of rhodium. Chauvin's group also reported a selective hydrogenation of 1,3-cyclohexadiene to cyclohexene (98% selectivity at 96% conversion) by taking advantage of the biphasic reaction system (**eq 1**):[24] the solubility of 1,3-cyclohexadiene in [BMIM][SbF_6] is about five times that of cyclohexene. It is worth noting that complete suppression of the hydrogenation activity was observed when ionic liquids containing Cl^- impurities were used.

Similarly, other rhodium- and cobalt-catalyzed hydrogenations, such as the hydrogenation of butadiene,[25] aromatic compounds,[26] or acrylonitrile–butadiene copolymers have been conducted successfully in ionic liquids.[27] More recently, a ruthenium-catalyzed stereoselective hydrogenation of sorbic acid to *cis*-3-hexenoic acid was performed in the biphasic [BMIM][PF_6]–MTBE system (**eq 2**).[28]

Enantioselective hydrogenation in ionic liquids has attracted special attention, since it provides a means for recycling metal complexes of expensive chiral ligands. In the presence of [Rh(cod)(–)-(diop)][PF_6] catalyst {cod = 1,3-cyclooctadiene; diop = 4,5-bis[(diphenylphosphanyl)methyl]-2,2-dimethyl-1,3-dioxolan-4,5-diol} in [BMIM][SbF_6], the enantioselective hydrogenation of α-acetamidocinnamic acid to (*S*)-phenylalanine was achieved with 64% enantiomeric excess (ee) (**eq 3**).[23]

Another successful example of enantioselective hydrogenation was reported by Monteiro et al., who used [$RuCl_2$(*S*)-BINAP]$_2$•NEt_3 as the chiral catalyst.[29] (*S*)-Naproxen was thus synthesized in 80% ee from 2-(6-methoxy-2-naphthyl)acrylic acid in [BMIM][BF_4] and isopropyl alcohol (**eq 4**).

Very recently, biphasic systems containing an ionic liquid and supercritical CO_2 ($scCO_2$) have been investigated for catalytic hydrogenation.[30,31] Tumas and co-workers[30] observed that the hydrogenation of olefins could be achieved in a biphasic [BMIM][PF_6]–$scCO_2$ system. The ionic liquid phase containing the catalyst was decanted and reused in up to four consecutive reactions. Jessop's group[31] performed the successful asymmetric hydrogenation of tiglic acid (**eq 5**) and the precursor of the anti-inflammatory drug ibuprofen (**eq 6**) by using Ru(OAc)$_2$((*R*)-tolBINAP) as catalyst. In both cases, the product was separated by $scCO_2$ extraction upon completion of the reaction.

Molecular hydrogen was found four times more soluble in [BMIM][BF_4] than in [BMIM][PF_6] at the same pressure.[32] Systematic studies of the effect of hydrogen concentration on enantioselectivity have been conducted by Berger et al. in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid and the kinetic resolution of methyl (±)-3-hydroxy-2-methylenebutanoate by Rh(I) and Ru(II) catalysts.[32] The concentration of molecular hydrogen in the ionic liquid rather than its pressure in the gas phase was found to have the most significant influence on the conversion and enantioselectivity of these reactions.

3.2. Oxidation

Although ionic liquids are highly stable and have been evaluated as media for oxidation reactions,[17] surprisingly little attention has been focused on carrying out catalytic oxidations in ionic liquids. A recent publication by Song and Roh is one of the earliest studies of catalytic oxidations in ionic liquids.[33] In this study, asymmetric Jacobsen–Katsuki epoxidations were performed with NaOCl in [BMIM][PF_6] and were catalyzed by a chiral Mn complex (Jacobsen's catalyst) (**eq 7**). A clear improvement of the catalytic activity was observed by adding the ionic liquid to the dichloromethane solvent. The ionic liquid containing the catalyst was reused in four consecutive runs without significant loss in yield; however, after the 5th run, the conversion dropped from 83% to 53%. This drop in conversion is believed to be due to a degradation of the [Mn^{III}(salen)] complex.

Another example of catalytic oxidation is the methyltrioxorhenium (MTO)-catalyzed epoxidation of olefins with the urea–H_2O_2 adduct (UHP) in [EMIM][BF_4].[34] High conversions and yields were observed, except for 1-decene (46% conversion, > 99% yield), which was attributed to its lower solubility in the ionic liquid. In the case of sensitive epoxides, ring opening was observed in the presence of large amounts of water.

A more exciting study utilized a chiral Mn(salen) complex in [BMIM][PF_6] for the electroassisted biomimetic activation of molecular oxygen.[35] It was observed that a highly reactive oxomanganese(V) intermediate could transfer its oxygen to an olefin, which hints at a promising future for clean oxidations with molecular oxygen in ionic liquid media.

3.3. Hydroformylation

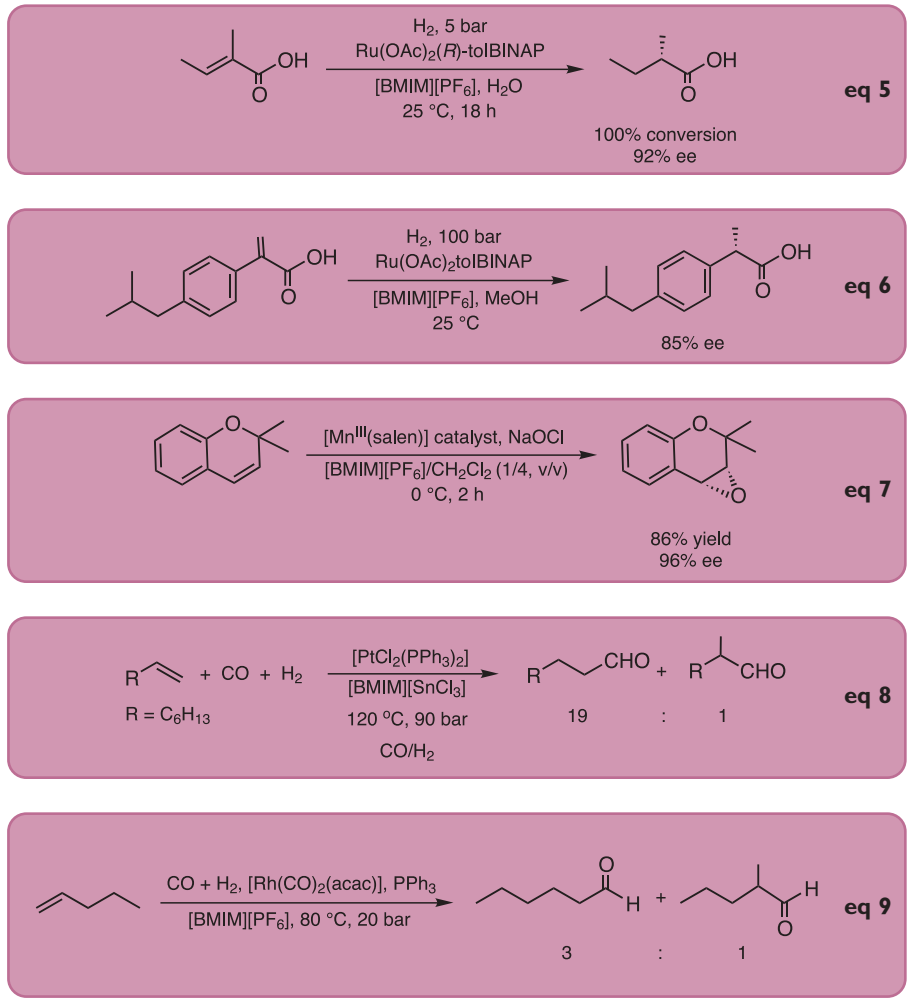
The platinum-catalyzed hydroformylation of ethene in tetraethylammonium trichlorostannate melts was conducted by Parshall as early as 1972.[36] The ionic liquid used in this case has a high melting point of 78 °C. Recently, Waffenschmidt and Wasserscheid reported the platinum-catalyzed hydroformylation of 1-octene in the room-temperature ionic liquid [BMIM][$SnCl_3$] (**eq 8**).[37] This biphasic system offered the advantage of simple product isolation and easy recovery of the platinum catalyst.

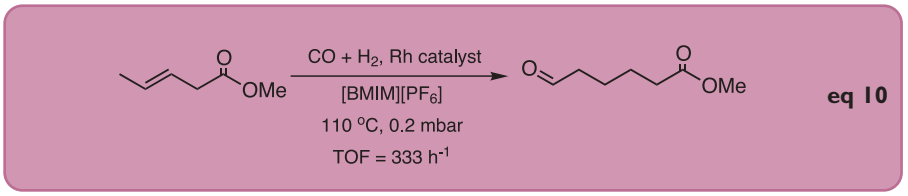
The ruthenium- and cobalt-catalyzed hydroformylation of internal and terminal alkenes in molten tetra-*n*-butylphosphonium bromide was reported by Knifton in 1987.[38] The rhodium-catalyzed hydroformylation of 1-hexene was investigated in higher-melting phosphonium tosylates, such as [Bu_3PEt][TsO] (mp 81–83 °C) and [Ph_3PEt][TsO] (mp 94–95 °C).[39] The product was easily separated from the solid catalyst medium at room temperature, and the catalyst was reused without loss of activity.

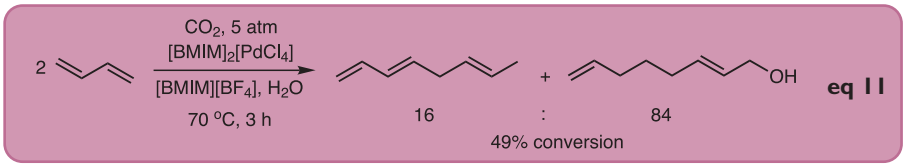
By employing room-temperature ionic liquid [BMIM][PF_6] as the reaction medium, the rhodium-catalyzed hydroformylation of 1-pentene was performed by Chauvin et al. (**eq 9**).[23] A higher activity [turnover frequency (TOF) = 333 h^{-1}] was observed as compared to the same reaction in toluene (TOF = 297 h^{-1}). Another report also indicated that a higher activity (TOF = 810 h^{-1}) and higher regioselectivity (*n/iso* = 16) were possible in the biphasic hydroformylation of 1-octene in [BMIM][PF_6] using a Rh-based catalyst.[40] Catalyst loss in the organic phase was less than 0.5%, and the ionic liquid catalyst solution was recycled. A high regioselectivity (20:1) was also obtained in the hydroformylation of 1-octene in [BMIM][PF_6] by using cationic guanidine-modified diphosphine ligands containing a xanthene backbone.[41]

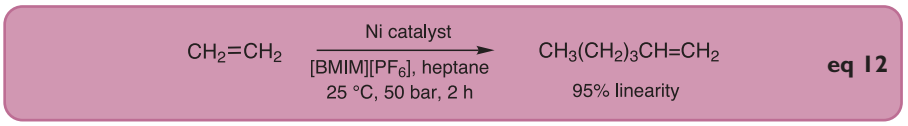
Not only have the biphasic hydroformylation reactions in ionic liquids shown their process advantages, but so has the rhodium-catalyzed monophasic reaction of methyl 3-pentenoate in [BMIM][PF_6] (**eq 10**).[42] The recovered catalyst was reused ten times under the same conditions without loss of activity.

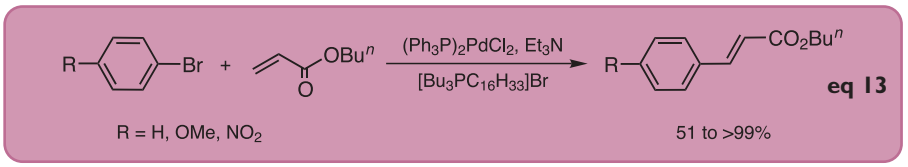
An interesting continuous flow process was utilized for the rhodium-catalyzed biphasic hydroformylation of 1-octene in [BMIM][PF_6]–$scCO_2$.[43] The product was synthesized at a fixed rate for 72 h with *n/iso* regioselectivity of 3.8, and only <1 ppm of Rh was lost in the organic phase.

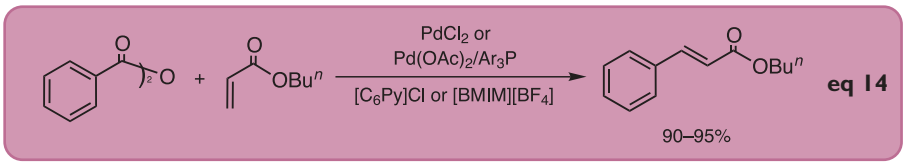


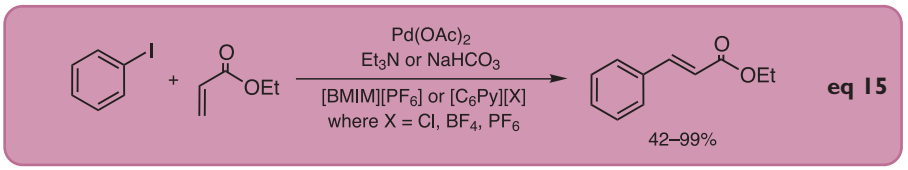












3.4. Hydrodimerization

Nickel(II)-catalyzed dimerization reactions in ionic liquids were first investigated in chloroaluminate(III) ionic liquid [BMIM][$AlCl_4$].[44] The product hexenes were separated from the ionic liquid by decantation. Due to the dissociation of ionic metal complexes caused by ionic liquids, it was believed that the ionic liquids were beneficial for the reactions. This application was extended to the oligomerization of butenes[45] and to the selective dimerization of ethene.[46]

Hydrodimerizations in ionic liquids can have many advantages over traditional hydrodimerizations, including higher selectivity for dimers due to their low solubility in ionic liquids, smaller reactor size, lower disposal costs, absence of corrosion, and wider applicability to less reactive and higher olefins.[15]

In recent years, chloroaluminate-free ionic liquids have become a new development in hydrodimerizations, because these new types of ionic liquids are more stable and easier to handle than the moisture-sensitive chloroaluminate(III) ionic melts. For example, [BMIM][BF_4] in water (1:1 v/v) was investigated in the hydrodimerization of 1,3-butadiene catalyzed by [BMIM]$_2$[$PdCl_4$].[47] In addition to the dimer, 1,3,6-octatriene, 2,7-octadienol was also produced (**eq 11**). However, by using $PdCl_2$/Ph_3P (1:4) as catalyst in [BMIM][X] (X = BF_4^-, PF_6^-, $CF_3SO_3^-$), the dimer, 1,3,6-octatriene, was obtained exclusively.[48]

Nickel(II)-catalyzed hydrodimerization reactions have also been studied in room-temperature ionic liquids. Wasserscheid and co-workers obtained a dimer selectivity of 98% and a TOF of 1240 h^{-1} at 25 °C in the linear dimerization (64% linearity) of 1-butene.[5,49] Recently, Wasserscheid, Gordon, and their co-workers also reported a biphasic oligomerization of ethene to higher α-olefins by nickel complexes in [BMIM][PF_6] (**eq 12**).[50] The product was separated easily as a clear layer, and the catalyst-containing ionic liquid layer was recovered without any detectable loss of catalyst activity.

3.5. Heck Reaction

The first use of ionic liquids as reaction media for the palladium-catalyzed Heck coupling was reported by Kaufmann et al. in 1996.[51] Moderate-to-high yields of butyl *trans*-cinnamates were obtained in molten tetraalkylammonium and tetraalkylphosphonium bromides by reaction of bromobenzenes with butyl acrylate (**eq 13**). The ionic liquid is believed to stabilize the palladium catalyst, and, in most reactions, no precipitation of palladium was observed even after complete conversion of the aromatic halide to the product.

Bohm and Hermann have extended this work to low-melting salts.[52] Their results indicate that molten [NBu_4][Br] (mp 103 °C) performs better in the Heck reaction than organic solvents such as DMF. In the reaction of bromobenzene with styrene, the yield of stilbene is increased from 20% in DMF to 99% in [NBu_4][Br] by using diiodobis(1,3-dimethylimidazolium-2-ylidene)palladium(II) as catalyst. Additional advantages of this solvent are the excellent solubility of all reacting molecules in it and its possible application as an inexpensive inorganic base. The authors also claim that the use of ionic liquids could become part of a standard method for carrying out Heck reactions in the future.

Earle, Seddon, and their co-workers described Heck couplings in [BMIM][PF_6] or *n*-hexylpyridinium hexafluorophosphate by using $PdCl_2$ or $Pd(OAc)_2$/Ar_3P as the catalyst (**eq 14**, **15**).[53] They reported a workup procedure in the three-phase system [BMIM][PF_6]/water/hexane. The products were soluble in the organic phase, while the used catalyst remained in the ionic layer. The salt formed as a by-product, [Hbase]X, dissolved in the aqueous phase.

The in situ identification of N-heterocyclic carbene complexes of palladium was performed by Xiao's group.[54] It was observed that [BMIM][Br] is more efficient in improving the Heck reaction rate than [BMIM][BF_4]. Two catalyst complexes, [PdBr(μ-Br)(bmiy)]$_2$ and [$PdBr_2$(bmiy)]$_2$, were isolated in [BMIM][Br] but not in [BMIM][BF_4] under the same reaction conditions. It was presumed that the stronger basicity of bromide as compared to tetrafluoroborate was a major factor in the formation of the carbene in [BMIM][Br]. Recently, Xiao and co-workers obtained >99% regioselectivity for the α-arylation

product in the Heck coupling of 1-bromonaphthalene with butyl vinyl ether in [BMIM][BF_4].[55] Similarly, [BMIM][BF_4] and [BMIM][PF_6] have also been employed in the palladium-catalyzed Stille[56] and Negishi couplings,[57] and in the nickel-catalyzed coupling of aryl halides.[58]

Other recent studies of the Heck coupling in ionic liquids include the Heck reaction of β-substituted acrylates in [NBu_4][Br] catalyzed by a palladium–benzothiazole carbene complex,[59] and the synthesis of pterocarpans by a Heck–oxyarylation reaction sequence in [BMIM][PF_6] in the presence of [$PdCl_2(PhCN)_2$]/Ph_3P/Ag_2CO_3 as the catalyst system.[60]

3.6. Alkoxycarbonylation

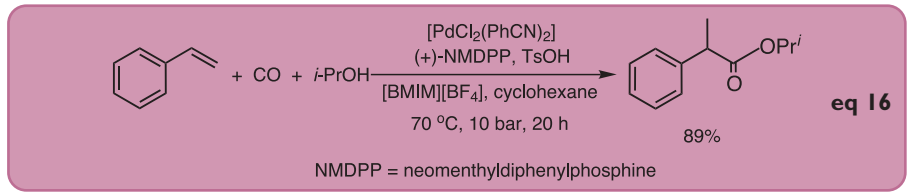
Carbonylation reactions in ionic liquids have received much less attention than the previously discussed transition-metal-catalyzed reactions. An example of palladium-catalyzed alkoxycarbonylation of styrene was reported by Monteiro and co-workers (**eq 16**).[61] In the reaction medium [BMIM][BF_4]/cyclohexane, styrene reacted with isopropyl alcohol and carbon monoxide to form isopropyl 2-phenylpropionate. Using (+)-neomenthyldiphenylphosphine [(+)-NMDPP] as ligand, the product was obtained in 89% yield and 99.5% regioselectivity, but with a very low asymmetric induction (ee < 5%).

A study of the palladium-catalyzed alkoxycarbonylation of aryl bromides and iodides in [BMIM][BF_4] and [BMIM][PF_6] was reported by Mizushima et al.,[62] who observed improved reactivities in the ionic liquids.

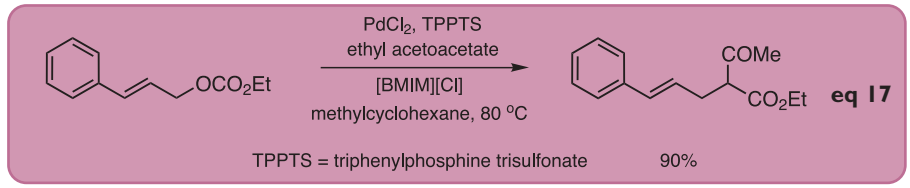
3.7. Trost–Tsuji Coupling

The Trost–Tsuji coupling is an important method for synthesizing carbon–carbon bonds through nucleophilic, allylic substitution. An interesting example is the monophasic reaction of 3-acetoxy-1,3-diphenylpropene with dimethyl malonate in [BMIM][BF_4].[63] The product is obtained in 91% yield after 5 h at room temperature using $Pd(OAc)_2$/PPh_3 as the catalyst system and K_2CO_3 as the base.

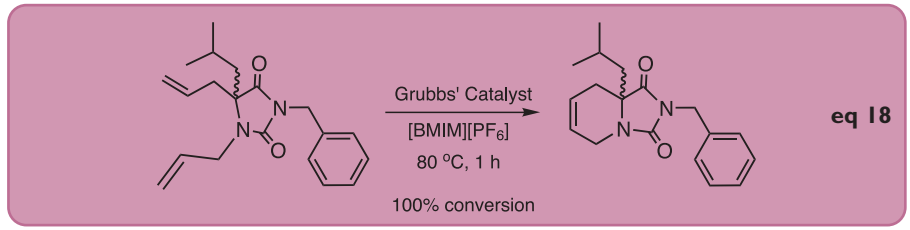
Biphasic Trost–Tsuji couplings have been conducted by de Bellefon et al. in [BMIM][Cl]/methylcyclohexane.[64] These workers observed a tenfold improvement in the catalytic activity due to the higher solubility of the substrates in the ionic liquid (**eq 17**). Enhanced selectivity was also achieved, since the formation of cinnamyl alcohol and phosphonium salts was suppressed.



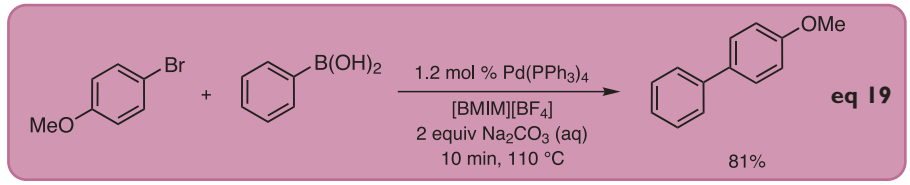
eq 16



eq 17



eq 18



eq 19

3.8. Ring-Closing Metathesis (RCM)

Ring-closing metathesis (RCM) is widely recognized as a powerful method for creating heterocycles, constrained peptides, and complex natural products.[65] [BMIM][PF_6] was used as an effective medium for ring-closing metathesis (RCM) that is induced by Grubbs' catalysts (**eq 18**).[66] After extraction of the product, [BMIM][PF_6] and the ruthenium catalyst were reused for three cycles. High conversions and a broad substrate tolerance were observed.

3.9. Suzuki Cross-Coupling

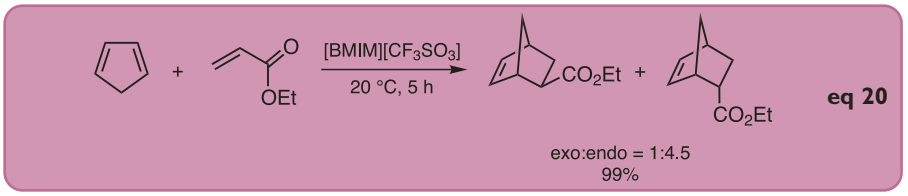
The Suzuki cross-coupling reaction is another versatile method for generating new carbon–carbon bonds. However, the traditional reaction suffers from several drawbacks such as incorporation of the catalyst into the product, decomposition of the catalyst, and/or poor reagent solubility. In order to overcome these drawbacks, a study of the palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids has recently been conducted in the room-temperature ionic liquid [BMIM][BF_4] (**eq 19**). Unprecedented reactivities were observed in addition to the easy isolation of product and recovery of catalyst.[67] This study identified several advantages of the Suzuki cross-coupling carried out in ionic liquids, namely: (a) a significant increase in reactivity is observed at a reduced catalyst concentration, especially for nonactivated aryl bromides; (b) homocoupling is avoided; (c) the reaction can be conducted under air without loss of yield or degradation of catalyst; and (d) repetitive runs can be performed without loss of catalyst activity.

4. Other Organic Reactions

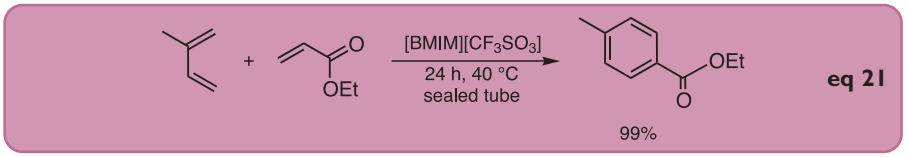
4.1. Diels–Alder Reaction

An early study of the Diels–Alder reaction of cyclopentadiene with methyl acrylate or methyl vinyl ketone in [$EtNH_3$][NO_3] was reported in 1989.[68] Although the reaction rate and selectivity were lower than those in water, the study showed that ionic liquids could be employed in this type of reaction. Encouraged by these findings, Diels–Alder reactions were conducted in several other ionic liquids such as [EMIM][PF_6],[69,70] [EMIM][BF_4],[70] [EMIM][CF_3SO_3],[70] [BMIM][ClO_4],[69] [EMIM][Cl]–$AlCl_3$,[71] and [BMIM][CF_3SO_3].[72] Two examples of these reactions are illustrated in **eq 20** and **21**.[72]

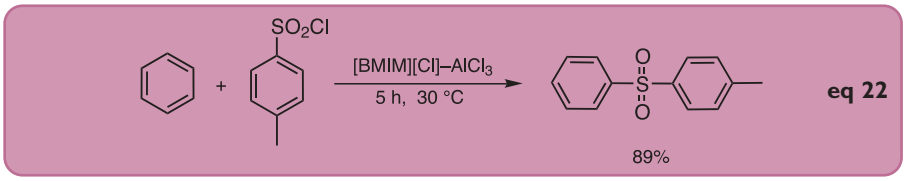
The use of $LiClO_4$ in diethyl ether has become one of the biggest developments in Diels–Alder chemistry. The $LiClO_4$–Et_2O



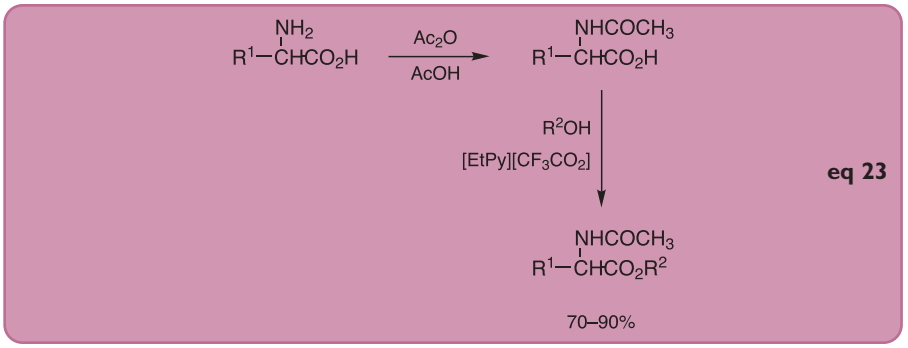
eq 20



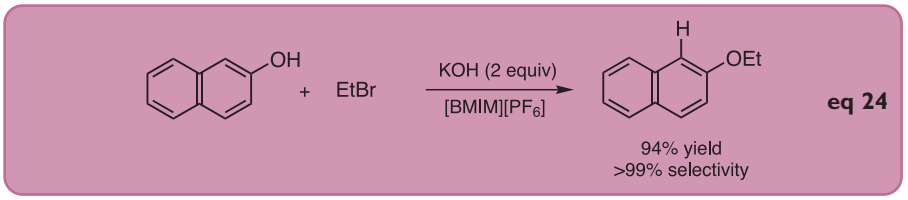
eq 21



eq 22



eq 23



eq 24

system can accelerate the Diels–Alder reaction due to the high concentration of electrolyte. By using ionic liquids instead of $LiClO_4$–Et_2O, reactivities can be improved and the need for potentially explosive perchlorate-based reaction media is eliminated.[72]

A recent study of the scandium triflate catalyzed Diels–Alder reaction investigated the use of ionic liquids as polar media for facilitating catalyst recovery and increasing reaction rate and selectivity.[73] For example, when 1,4-naphthoquinone was dissolved in [BMIM][PF_6] and reacted with 1,3-dimethylbutadiene in the presence of $Sc(OTf)_3$, the corresponding product was obtained in > 99% yield.

4.2. Friedel–Crafts Reaction

Friedel–Crafts acylations are of industrial importance and are associated with a massive consumption of aluminum(III) chloride. It has been demonstrated that acylation reactions can be carried out in acidic chloroaluminate(III) ionic liquids.[74,75] The regioselectivities and rates observed in these reactions are comparable to the best values known for the traditional acylations. The Friedel–Crafts acylation of benzene has been conducted in acidic chloroaluminate(III) ionic liquid.[75] The monoacylated products were obtained as a result of the deactivation of the aromatic ring by the acyl substituent. In addition to benzene and other simple aromatic rings, a range of organic and organometallic substrates (e.g., ferrocene) have been acylated in acidic chloroaluminate(III) ionic liquids.[76,77]

An in situ IR spectroscopic study was performed on the Friedel–Crafts acetylation of benzene in ionic liquids using $AlCl_3$ and $FeCl_3$.[78] The results revealed that the mechanism of the Friedel–Crafts acetylation of benzene in ionic liquids was exactly the same as that in 1,2-dichloroethane.

Another interesting development is the use of [BMIM][chloroaluminate] as Lewis acid catalyst for the Friedel–Crafts sulfonylation of benzene and substituted benzenes with TsCl (**eq 22**).[79] The substrates exhibited enhanced reactivity, and furnished the corresponding unsymmetrical diaryl sulfones in 83–91% yields under ambient conditions.

4.3. Esterification

Esterifications of alcohols and acetic acids in the room-temperature ionic liquid 1-butylpyridinium chloride–aluminum(III) chloride as a "green" catalyst have been reported by Deng et al.[80] Satisfactory conversions and selectivities were obtained, and most of the ester products were easily recovered due to their immiscibility with the ionic liquid.

Amino acid esters are very important intermediates in the chemical and pharmaceutical industry. They are usually difficult to prepare because amino acids exist as zwitterions (dipolar ions), in which the carboxyl group is not in the free form. Our group has recently developed a successful method for synthesizing amino acid esters using [EtPy][CF_3CO_2] (EtPy = *N*-ethylpyridinium) as a "green" catalyst.[81] Excellent conversions have generally been achieved for the ethyl and isopropyl esters of many amino acids (**eq 23**).

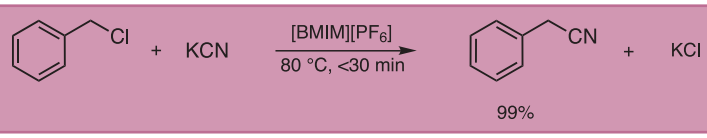
4.4. Regioselective Alkylation

Alkylation of indole or 2-naphthol is usually achieved by preformation of the ambident indolate[82] or 2-naphtholate[83] anion and subsequent treatment with alkyl halide. Regioselective alkylation at the heteroatom of these anions is solvent-dependent, and can be achieved by using a dipolar aprotic solvent such as DMF.[83,84] As an environmentally friendly alternative, [BMIM][PF_6] has been utilized for the regioselective alkylation at the heteroatom of indole and 2-naphthol (**eq 24**).[85] Advantages of this process include simple operation, easy product isolation, no measurable solvent vapor pressure, high regioselectivity, and the potential for recycling the solvent.

4.5. Displacement Reaction with Cyanide

Nucleophilic displacement reactions are often achieved using phase-transfer catalysis (PTC) to facilitate reaction between the organic reactants and the inorganic ionic

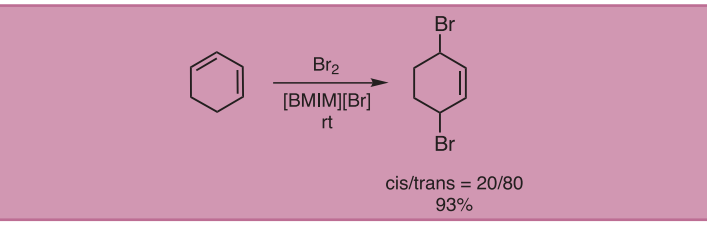
salts that provide the nucleophiles.[86] In conventional PTC, the typical organic solvents used, such as dichloroethane or *o*-dichlorobenzene, are environmentally undesirable. In addition, catalyst separation and recovery are very difficult. It has been demonstrated that the use of room-temperature ionic liquids as catalytic, environmentally benign solvents for the displacement of benzylic chloride with cyanide can replace phase-transfer-catalyzed biphasic systems (**eq 25**).[87] This eliminates the need for a volatile organic solvent and hazardous catalyst disposal.



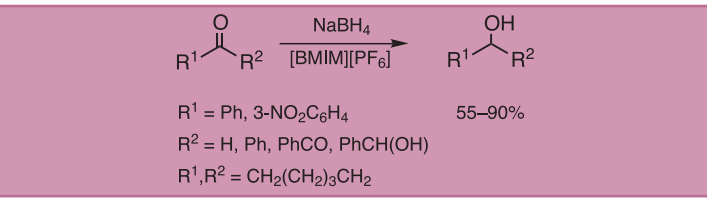
eq 25

4.6. Stereoselective Halogenation

The analysis of alkenes in a complex hydrocarbon mixture, such as gasoline, is a difficult process. The analysis of alkenes in the presence of alkanes, however, can be achieved after their transformation into the corresponding dihalo derivatives.[88] Several ionic liquids—[BMIM][PF_6], [BMIM][BF_4], [BMIM][Br], and [BMIM][Cl]—have been studied as alternatives to toxic chlorinated solvents for the stereoselective halogenation of alkenes and alkynes (**eq 26**).[89]



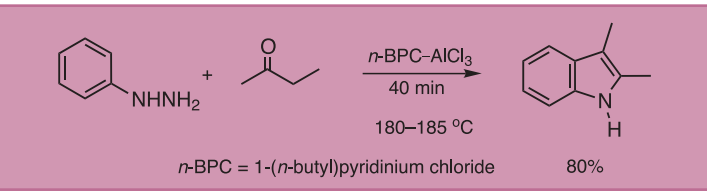
eq 26



eq 27

4.7. Reduction of Aldehydes and Ketones

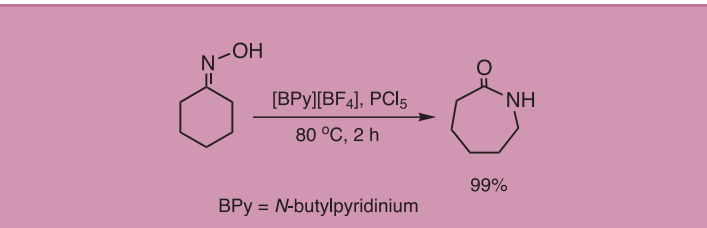
Howarth et al. have investigated the reduction of aldehydes and ketones with $NaBH_4$ in [BMIM][PF_6].[90] In this study, six common aldehydes and ketones were converted into the corresponding alcohols in moderate-to-high yields (**eq 27**). The ionic liquid was recycled, and, in some cases, the product alcohol was distilled directly from the ionic liquid.



eq 28

4.8. Fischer Indole Synthesis

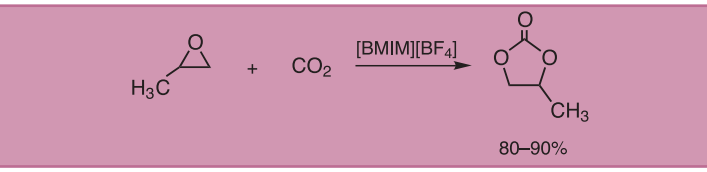
The Fischer indole synthesis using a chloroaluminate ionic liquid both as a solvent and catalyst was achieved with product yields in the 41–92% range (**eq 28**).[91] The amount of $AlCl_3$ used was much less than that of other reported catalysts such as $ZnCl_2$ or PPA, and the procedure followed proved safer with respect to the amount of catalyst employed, its hazard, and cost.



eq 29

4.9. Beckmann Rearrangement

The Beckmann rearrangement is typically carried out in strong Brønsted or Lewis acids, such as concentrated sulfuric acid, phosphorus pentachloride in ether, or hydrogen chloride in a mixture of acetic acid and acetic anhydride. These conditions give rise to significant amounts of by-products and serious corrosion problems.[92] In a recent study by Peng and Deng,[93] the catalytic Beckmann rearrangement of several ketoximes was achieved with satisfactory conversion and selectivity in 1,3-dialkyl-imidazolium or alkylpyridinium salts and phosphorated compounds (PCl_5, $POCl_3$, or P_2O_5) (**eq 29**).



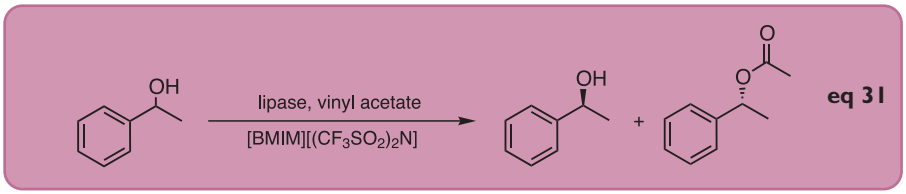
eq 30

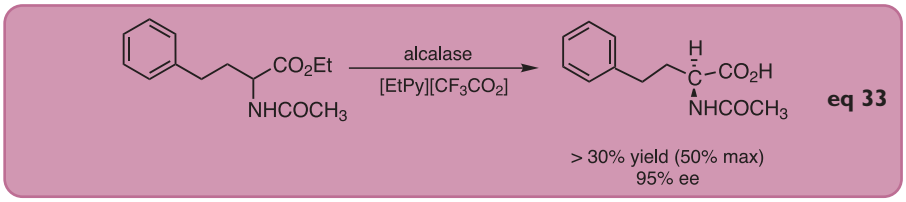
4.10. Cycloaddition

The cycloaddition of propylene oxide (PO) and carbon dioxide has been conducted in ionic liquids based on [BMIM] or [BPy] salts and in the absence of any organic solvent. Optimal results were obtained with [BMIM][BF_4] as catalyst (**eq 30**).[94] It was found that both the cations and anions of the room-temperature ionic liquids exerted a strong influence on catalytic activity, and a suitable CO_2/PO molar ratio was required for the reaction. The conversion of propylene oxide increased with increasing reaction temperature, and the ionic liquid catalyst was recycled.

5. Biocatalysis in Ionic Liquids

In recent years, a lot of attention has been focused on enzymatic reactions in ionic liquids. As early as 1984, it was observed that the enzyme alkaline phosphatase is relatively stable in a 4:1 (v/v) mixture of triethylammonium nitrate and water.[95] Erbeldinger et al. reported the first enzymatic synthesis of *Z*-aspartame in [BMIM][PF_6] containing 5% (v/v) water.[96] The enzyme





thermolysin exhibited excellent stability and a competitive rate in the same ionic liquid as compared to the enzymatic reaction in organic solvents.

Lipase has frequently been reported as a biocatalyst of organic reactions in ionic liquids. Nine lipases were investigated for the dynamic kinetic resolution of 1-phenylethanol by transesterification in various ionic liquids.[97] Improved enantioselectivities were observed as compared to when these same reactions were carried out in MTBE (**eq 31**). Kim et al. also obtained enhanced enantioselectivities in the transesterifications of alcohols using lipase in [BMIM][BF_4] and [BMIM][PF_6].[98] In the lipase-catalyzed enantioselective acylation of allylic alcohols in [BMIM][X] (X = PF_6^-, $CF_3CO_2^-$, TsO^-, SbF_6^-), Itoh et al. found that the anions of the imidazolium salts had a significant influence on the outcome of the reaction (**eq 32**).[99]

More systematic studies on lipase-catalyzed enantio- and regioselective acylations were conducted by Park and Kazlauskas in several imidazolium- and *N*-alkylpyridinium-based ionic liquids.[100] In these studies, the *Pseudomonas cepacia* lipase (PCL) catalyzed acylation of 1-phenylethanol with vinyl acetate proceeded with high enantioselectivity. Regioselective acetylation of β-D-glucose in ionic liquids yielded more 6-*O*-acetylglucose than 3,6-*O*-diacetylglucose (13–50:1), while the acetylation in organic solvents gave a selectivity of only 2–3:1. The epoxidation of cyclohexene by peroxyoctanoic acid, generated in situ by the immobilized enzyme Novozyme® 435 catalyzed reaction of octanoic acid with 60% aqueous H_2O_2, was achieved successfully.[101] Another study showed that the enantioselectivity of a lipase-catalyzed kinetic resolution could be increased at higher temperatures.[102] This study indicated that, for a galactosidase-catalyzed synthesis of a disaccharide, the secondary hydrolysis was suppressed thus doubling the yield. It was also observed that three different lipases exhibited both excellent activity and stability in the synthesis of an ester in [BMIM][PF_6].[103]

Recently, we showed that high enantioselectivities and yields could be achieved in the kinetic resolution of amino acid esters such as that of homophenylalanine in [EtPy][CF_3CO_2] by using the enzyme *Bacillus licheniforms* alcalase (**eq 33**).[104] This same alcalase also exhibited high selectivity and activity in low concentrations of ionic liquid in water.

6. Summary

The use of ionic liquids as solvents or catalysts has a profound effect on the observed activities and selectivities. As a result, there is growing interest in developing applications for them in a wide range of synthetic reactions. The present review was not designed to be comprehensive, but rather to summarize some of the recent advances in the application of ionic liquids in organic synthesis. We hope that readers will find it helpful in their day-to-day work.

7. References and Notes

(†) This review is dedicated to Professor Herbert C. Brown on his 90th birthday.

(1) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351.

(2) Hurley, F. H.; Wier, T. P. *J. Electrochem. Soc.* **1951**, *98*, 203.

(3) (a) Wilkes, J. S.; Levisky, J. A.; Wilson, R. A.; Hussey, C. L. *Inorg. Chem.* **1982**, *21*, 1263. (b) Wilkes, J. S.; Zaworotko, M. J. *J. Chem. Soc., Chem. Commun.* **1992**, 965.

(4) Freemantle, M. *Chem. Eng. News* **1998**, *76(13)*, 32.

(5) Wasserscheid, W.; Keim, W. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3772.

(6) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.

(7) Cull, S. G.; Holbrey, J. D.; Vargas-Mora, V.; Seddon, K. R.; Lye, G. J. *Biotechnol. Bioeng.* **2000**, *69*, 227.

(8) Fuller, J.; Breda, A. C.; Carlin, R. T. *J. Electroanal. Chem.* **1998**, *459*, 29.

(9) Kosmulski, M.; Osteryoung, R. A.; Ciszewska, M. *J. Electrochem. Soc.* **2000**, *147*, 1454.

(10) Bates, E. D.; Mayton, R. D.; Ntai, I.; Davis, J. H., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 926.

(11) Sheng, D.; Ju, Y. H.; Barnes, C. E. *J. Chem. Soc., Dalton. Trans.* **1999**, 1201.

(12) Fadeev, A. G.; Meagher, M. M. *Chem. Commun.* **2001**, 295.

(13) Brennecke, J. F.; Maginn, E. J. *AIChE J.* **2001**, *47*, 2384.

(14) Fuller, J.; Carlin, R. T.; De Long, H. C.; Haworth, D. *J. Chem. Soc., Chem. Commun.* **1994**, 299.

(15) Chauvin, Y.; Olivier-Bourbigou, H. *CHEMTECH* **1995**, *25*(9), 26.

(16) Keim, W.; Korth, W.; Wasserscheid, P. Intl. Patent 0016,902, Mar 30, 2000; *Chem. Abstr*. **2000**, *132*, P 238691v.

(17) Bonhôte, P.; Dias, A.-P.; Papageorgiou, N.; Kalyanasundaram, K.; Grätzel, M. *Inorg. Chem.* **1996**, *35*, 1168.

(18) Ford, W. T.; Hauri, R. J.; Hart, D. J. *J. Org. Chem.* **1973**, *38*, 3916.

(19) Karodia, N.; Guise, S.; Newlands, C.; Andersen, J.-A. *Chem. Commun*. **1998**, 2341.

(20) Hasan, M.; Kozhevnikov, I. V.; Siddiqui, M. R. H.; Steiner, A.; Winterton, N. *Inorg. Chem.* **1999**, *38*, 5637.

(21) Fannin, A. A.; Floreani, D. A.; King, L. A.; Landers, J. S.; Piersma, B. J.; Stech, D. J.; Vaughn, R. L.; Wilkes, J. S.; Williams, J. L. *J. Phys. Chem.* **1984**, *88*, 2614.

(22) Larsen, A. S.; Holbrey, J. D.; Tham, F. S.; Reed, C. A. *J. Am. Chem. Soc.* **2000**, *122*, 7264.

(23) Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698.

(24) Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem*. **1995**, *107*, 2941.

(25) Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. *Inorg. Chim. Acta* **1997**, *255*, 207.

(26) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun*. **1999**, 25.

(27) Muller, L. A.; Dupont, J.; de Souza, R. F. *Makromol. Chem., Rapid Commun*. **1998**, *19*, 409.

(28) Steines, S.; Drieben-Holscher, J.; Wasserscheid, P. *J. Prakt. Chem*. **2000**, *342*, 348.

(29) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177.

(30) Liu, F.; Abrams, M. B.; Baker, R. T.; Tumas, W. *Chem. Commun*. **2001**, 433.

(31) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc*. **2001**, *123*, 1254.
(32) Berger, A.; de Souza, R. F.; Delgado, M. R.; Dupont, J. *Tetrahedron: Asymmetry*. **2001**, *12*, 1825.
(33) Song, C. E.; Roh, E. J. *Chem. Commun*. **2000**, 837.
(34) Owens, G. S.; Abu-Omar, M. M. *Chem. Commun*. **2000**, 1165.
(35) Gaillon, L.; Bedioui, F. *Chem. Commun*. **2001**, 1458.
(36) Parshall, G. W. *J. Am. Chem. Soc*. **1972**, *94*, 8716.
(37) Waffenschmidt, H.; Wasserscheid, P. *J. Mol. Catal. A: Chem*. **2000**, *164*, 61.
(38) Knifton, J. F. *J. Mol. Catal*. **1987**, *43*, 65.
(39) Karodia, N.; Guise, S.; Newlands, C.; Andersen, J.-A. *Chem. Commun*. **1998**, 2341.
(40) Brasse, C. C.; Englert, U.; Salzer, A.; Waffenschmidt, H.; Wasserscheid, P. *Organometallics* **2000**, *19*, 3818.
(41) Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper, K. W.; Stielzer, O. *Chem. Commun*. **2001**, 4510.
(42) Keim, W.; Vogt, D.; Waffenschmidt, H.; Wasserscheid, P. *J. Catal*. **1999**, *186*, 481.
(43) Sellin, M. F.; Webb, P. B.; Cole-Hamilton, D. J. *Chem. Commun*. **2001**, 781.
(44) Chauvin, Y.; Gilbert, B.; Guibard, I. *J. Chem. Soc., Chem. Commun*. **1990**, 1715.
(45) Chauvin, Y.; Olivier, H.; Wyrvalski, C. N.; Simon, L. C.; de Souza, R. F. *J. Catal*. **1997**, *165*, 275.
(46) Einloft, S.; Dietrich, F. K.; de Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 3257.
(47) Dullius, J. E. L.; Suarez, P. A. Z.; Einloft, S.; de Souza, R. F.; Dupont, J.; Fischer, J.; De Cian, A. *Organometallics* **1998**, *17*, 815.
(48) Silva, S. M.; Suarez, P. A. Z.; de Souza, R. F.; Dupont, J. *Polym. Bull*. **1998**, *40*, 401.
(49) Ellis, B.; Keim, W.; Wasserscheid, P. *Chem. Commun*. **1999**, 337.
(50) Wasserscheid, P.; Gordon, C. M.; Hilgers, C.; Muldoon, M. J.; Dunkin, I. R. *Chem. Commun*. **2001**, 1186.
(51) Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091.
(52) Bohm, V. P. W.; Hermann, W. A. *Chem. Eur. J*. **2000**, *6*, 1017.
(53) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett*. **1999**, *1*, 997.
(54) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123.
(55) Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett*. **2001**, *3*, 295.
(56) Handy, S. T.; Zhang, X. *Org. Lett*. **2001**, *3*, 233.
(57) Sirieix, L.; Ossberger, M.; Betzemeier, B.; Knochel, P. *Synlett* **2000**, 1613.
(58) Howarth, J.; James, P.; Dai, J. *Tetrahedron Lett*. **2000**, *41*, 10319.
(59) Calo, V.; Nacci, A.; Monopoli, A.; Lopez, L.; di Cosmo, A. *Tetrahedron* **2001**, *57*, 6071.
(60) Kiss, L.; Papp, G.; Joo, F.; Antus, S. *Heterocycl. Commun*. **2001**, *7*, 417.
(61) Zim, D.; de Souza, R. F.; Dupont, J.; Monteiro, A. L. *Tetrahedron Lett*. **1998**, *39*, 7071.
(62) Mizushima, E.; Hayashi, T.; Tanake, M. *Green Chem*. **2001**, *3*, 76; *Chem. Abstr.* **2001**, *136*, 118248.
(63) Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun*. **1999**, 1247.
(64) de Bellefon, C.; Pollet, E.; Grenouillet, P. *J. Mol. Catal*. **1999**, *145*, 121.
(65) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(66) Buijsman, R. C.; van Vuuren, E.; Sterrenburg, J. G. *Org. Lett.* **2001**, *3*, 3785.
(67) Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun*. **2000**, 1249.
(68) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785.
(69) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.
(70) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem*. **1999**, *1*, 23; *Chem. Abstr.* **1999**, *131*, 87674.
(71) Lee, C. W. *Tetrahedron Lett*. **1999**, *40*, 2461.
(72) Holbrey, J. D.; Seddon, K. R. *Clean Prod. Proc*. **1999**, *1*, 223.
(73) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.-g.; Choi, J. H. *Chem. Commun*. **2001**, 1122.
(74) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. *Chem. Commun*. **1998**, 2097.
(75) Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480.
(76) Surette, J. K. D.; Green, L.; Singer, R. D. *J. Chem. Soc., Chem. Commun*. **1996**, 2753.
(77) Dyson, D. J.; Grossle, M. C.; Srinivasan, N.; Vine, T.; Welton, T.; Williams, D. J.; White, A. J. P.; Zigras, T. *J. Chem. Soc., Dalton Trans*. **1997**, 3465.
(78) Csihony, S.; Mehdi, H.; Horvath, I. T. *Green Chem*. **2001**, *3*, 307.
(79) Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem*. **2001**, *66*, 8616.
(80) Deng, Y.; Shi, F.; Beng, J.; Qiao, K. *J. Mol. Catal. A: Chem*. **2001**, *165*, 33.
(81) Zhao, H.; Malhotra, S. V. Esterification of Amino Acids by Using Ionic Liquid as a Green Catalyst. In *Catalysis of Organic Reactions*; Morrell, D., Ed.; Marcel Dekker: New York, 2002; Volume 83; pp 667-672.
(82) Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 111.
(83) Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc*. **1963**, *85*, 1148.
(84) Cardillo, B.; Casnati, G.; Pochini, A.; Ricca, A. *Tetrahedron* **1967**, *23*, 3771.
(85) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Chem. Commun*. **1998**, 2245.
(86) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman and Hall: New York, 1994.
(87) Wheeler, C.; West, K. N.; Liotta, C. L.; Eckert, C. A. *Chem. Commun*. **2001**, 887.
(88) Delaet, M.; Tilquin, B. *Talanta* **1992**, *39*, 769.
(89) Chiappe, C.; Capraro, D.; Conte, V.; Pieraccini, D. *Org. Lett*. **2001**, *3*, 1061.
(90) Howarth, J.; James, P.; Ryan, R. *Synth. Commun*. **2001**, *31*, 2935.
(91) Rebeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370.
(92) Izumi, Y.; Sato, S.; Urabe, K. *Chem. Lett.* **1983**, 1649.
(93) Peng, J.; Deng, Y. *Tetrahedron Lett*. **2001**, *42*, 403.
(94) Peng, J.; Deng, Y. *Cuihua Xuebao* **2001**, *22*, 598; *Chem. Abstr.* **2002**, *136*, 218602.
(95) Magnusson, D. K.; Bodley, J. W.; Adams, D. F. *J. Solution Chem*. **1984**, *13*, 583.
(96) Erbeldinger, M.; Mesiano, A. J.; Russell, A. J. *Biotechnol. Prog*. **2000**, *16*, 1129.
(97) Schoefer, S. H.; Kaftzik, N.; Wasserscheid, P.; Kragl, U. *Chem. Commun*. **2001**, 425.
(98) Kim, K.-W.; Song, B.; Choi, M.-Y.; Kim, M.-J. *Org. Lett*. **2001**, *3*, 1507.
(99) Itoh, T.; Akasaki, E.; Kudo, K.; Shirakami, S. *Chem. Lett*. **2001**, 262.
(100) Park, S.; Kazlauskas, R. J. *J. Org. Chem*. **2001**, *66*, 8395.
(101) Langer, R.; Klausener, A.; Rodefeld, L. Intl. Patent Appl. W0 01 02,596, Jan 11, 2001; *Chem. Abstr.* **2001**, *134*, 85168u.
(102) Kragl, U.; Kaftzik, N.; Schoefer, S. H.; Eckstein, M.; Wasserscheid, P.; Hilgers, C. *Chim. Oggi*. **2001**, *19*(7/8), 22.
(103) Husum, T. L.; Jorgensen, C. T.; Christensen, M. W.; Kirk, O. *Biocatal. Biotransform.* **2001**, *19*, 331.
(104) Zhao, H.; Malhotra, S. V. *Biotechnol. Lett*. **2002**, *24*, 1257.

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Sanjay Malhotra was born in New Delhi, India. He received a Bachelor of Science degree from Gujrat University, India. After three years of industrial experience as an R&D scientist working on agrochemicals, he moved to the U.S. for further studies. He obtained a Ph.D. in 1995 from Seton Hall University under the direction of Professor Robert L. Augustine. Subsequently, he moved to Purdue University to work with Professor Herbert C. Brown, and spent the next four years as his research associate. In 1999, he joined the faculty of the New Jersey Institute of Technology. His research interests include the development of new methodologies and catalysts for asymmetric organic transformations. He is also active in research on ionic liquids, especially the study of enzymatic reactions in ionic liquids. He has authored several publications in the area of asymmetric catalysis, heterogeneous catalysts, and enzymatic reactions in ionic liquids. He is currently working on a book on new methodologies in asymmetric catalysis.

Hua Zhao received both his B.S. degree in chemistry and M.S. degree in chemical engineering from Tianjin University (China). In 2002, he obtained his Ph.D. degree in chemical engineering from the New Jersey Institute of Technology under the direction of Professor Sanjay Malhotra. His research interests are focused on the study of ionic liquids in enzymatic reactions.

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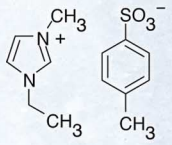
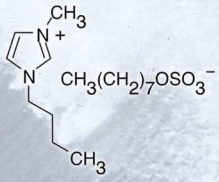
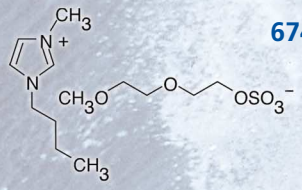


89155 1-Ethyl-3-methylimidazolium tosylate, [EMIM][Ts], purum, ≥98.0%
M_w 282.35 $C_{13}H_{18}N_2O_3S$ 5g; 50g



75059 1-Butyl-3-methylimidazolium octyl sulfate, [BMIM][$OctSO_4$], purum, ≥98.0%
M_w 348.50 $C_{16}H_{32}N_2O_4S$ 5g; 50g



67421 1-Butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate, [BMIM][$MEESO_4$], ≥98.0%
M_w 338.42 $C_{13}H_{26}N_2O_6S$ 5g; 50g

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39056 1-Ethyl-3-methylimidazolium bis(pentafluoroethylsulfonyl)imide, [EMIM][BEtI], purum, ≥97.0%
M_w 491.33 [216299-76-2] $C_{10}H_{11}F_{10}N_3O_4S_2$ 1g; 5g

11291 1-Ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imidate, [EMIM][BMeI], purum, ≥97.0%
M_w 391.31 [174899-82-2} $C_8H_{11}F_6N_3O_4S_2$ 1g; 5g

50807 1,2-Dimethyl-3-propylimidazolium bis(trifluoromethylsulfonyl)imide, [DMPIM][BMeI], purum, ≥97.0%
M_w 419.36 [169051-76-7] $C_{10}H_{15}F_6N_3O_4S_2$ 1g; 5g

14654 1-Butyl-3-methylpyridinium bis(trifluoromethylsulfonyl)imide, [BMPy][BMeI], purum, ≥97.0%
M_w 316.40 [344790-86-9] $C_{12}H_{16}N_2O_4S_2$ 1g; 5g

30565 3-Methyl-1-propylpyridinium bis(trifluoromethylsulfonyl)imide, [PMPy][BMeI], purum, ≥97.0%
M_w 302.37 $C_{11}H_{14}N_2O_4S_2$ 1g; 5g

74305 1,2-Dimethyl-3-propylimidazolium tris(trifluoromethylsulfonyl)methide, [DMPIM][TMeM], purum, ≥97.0%
M_w 550.44 [169051-77-8] $C_{12}H_{15}F_9N_2O_6S_3$ 1g; 2.5g

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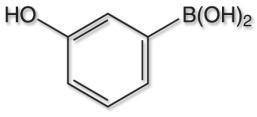
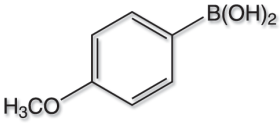
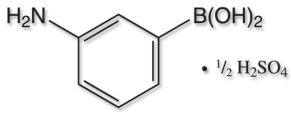


52,396-8 3-Hydroxyphenylboronic acid
CAS # 87199-18-6
MDL # 1074603



41,759-9 4-Methoxyphenylboronic acid
CAS # 5720-07-0
MDL # 39139



A7,175-1 3-Aminophenylboronic acid hemisulfate
CAS # 66472-86-4
MDL # 13111

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Indium tin oxide (ITO) is electrically conductive and transparent in the near-IR to UV range (≈300 nm to >2600 nm). Due to its optical transparency (85–90% transmission in the visible range), ITO-coated glass slides are ideal electrodes for the hole-injecting contact in optical light-emitting diodes (OLEDs).[1-3] The sensitivity of visible spectroelectrochemical instruments can be increased 200 times or more using ITO slides in an integrated optical waveguide.[4] ITO slides are useful deposition substrates for optoelectric materials[5] and liquid crystal displays.[6] Phosphor-coated indium tin oxide plates are also used in flat panel displays.[7] Aldrich now offers indium tin oxide coated float glass and aluminosilicate glass slides.

57,635-2 **Indium tin oxide coated glass slide**, 70–100-ohm resistance

57,827-4 **Indium tin oxide coated glass slide**, 8–12-ohm resistance

57,636-0 **Indium tin oxide coated aluminosilicate slide**, 5–15-ohm resistance

Product Number	57,635-2, 57,827-4	57,636-0
Slide Dimensions	25 x 75 x 1.1 mm	25 x 75 x 1.1 mm
Refractive Index	1.517	1.5290–1.5460
Strain Point	523 °C	666 °C
Typical Composition	72.6% SiO_2, 0.8% B_2O_3, 1.7% Al_2O_3, 4.6% CaO, 3.6% MgO, and 15.2% Na_2O	55.0% SiO_2, 7.0% B_2O_3, 10.4% Al_2O_3, 21.0% CaO, and 1.0% Na_2O
Passivation	passivated with 200+ Å SiO_2 applied directly to the glass slide prior to coating with ITO	no passivation layer is used, the ITO is applied directly to the substrate

Resistance is a factor of ITO thickness:

- 70–100 ohms = 150–300 Å ITO coating with a typical transmittance of 87%.

  Resistance may increase to as high as 375 ohms when exposed to temperatures of 300 °C for 30 minutes or more.

- 5–15 ohms = 1200–1600 Å ITO coating with a typical transmittance of 84%.

  Resistance may increase to as high as 30 ohms when exposed to temperatures of 300 °C for 30 minutes or more.

(1) Yan, C. et al. *Langmuir* **2000**, *16*, 6208. (2) Purvis, K.L. et al. *J. Am. Chem. Soc.* **2000**, *122*, 1808. (3) Biyikli, N. et al. *Appl. Phys. Lett.* **2001**, *79*, 2838. (4) Itoh, K. et al. *J. Phys. Chem.* **1988**, *92*, 7043. (5) Moriguchi, I. et al. *Chem. Mater.* **1998**, *10*, 2005. (6) Amako, J. et al. *Opt. Rev.* **1998**, *5*, 83. (7) Choi, W.B. et al. *Appl. Phys. Lett.* **1999**, *75*, 3129.

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Novel Methods of Resolving Racemic Diols and Amino Alcohols

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Outline

1. Introduction

In recent years, chiral amino alcohols and diols such as **1**[1,2], **2**,[3] and **3**[4] have been widely used as ligands to prepare catalysts employed in asymmetric synthesis. Whereas (*S*)-diphenylprolinol (**1**) and the chiral TADDOL derivative **2** can be readily synthesized starting from naturally occurring (*S*)-proline and (*R,R*)-tartaric acid, respectively, the widely used bi-2-naphthol (**3**) cannot be prepared starting from such natural chiral pool building blocks. Moreover, both enantiomers of any required starting material are generally not available from natural sources. Accordingly, there have been sustained efforts to develop synthetic methods for such useful chiral diols and amino alcohols.

While an asymmetric transformation may be contemplated for a crucial step in a multistep synthesis, the preparation of a racemic mixture followed by resolution can still be a viable and straightforward alternative, especially when both enantiomers are required. In recent years, very little effort has been made toward the development of new resolution methods for obtaining enantiomerically pure organic compounds, as compared to the immense efforts that have been spent toward the development of new asymmetric synthetic methods. Accordingly, we have undertaken research aimed at developing new resolution methods for diols and amino alcohols in order to facilitate the synthetic applications of these important compounds. In this review, recent developments in the methods of synthesis and resolution of some chiral diols and amino alcohols are surveyed.

2. Racemic Diols

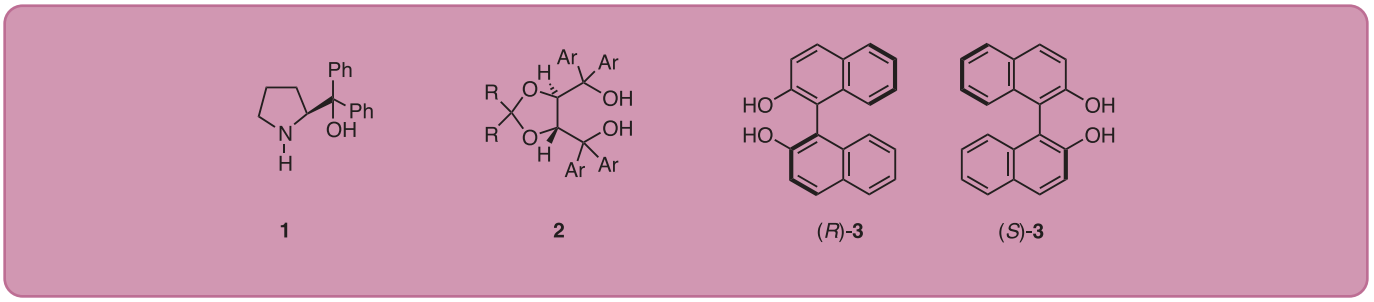
2.1. Resolution of Bi-2-naphthol

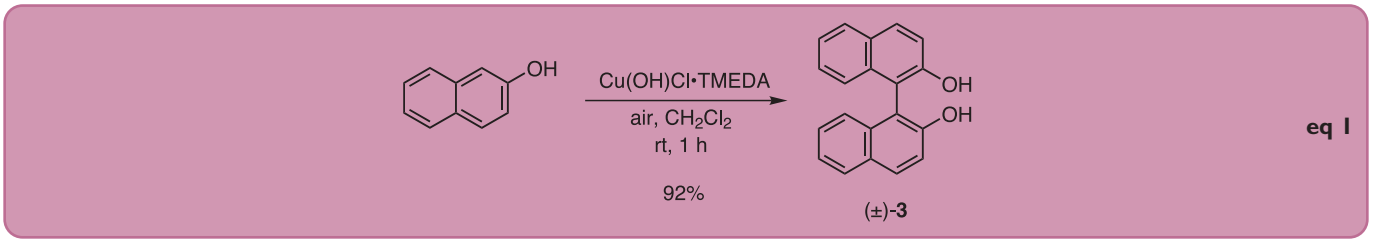
2.1.1. Via Diastereomeric Cyclic Phosphates

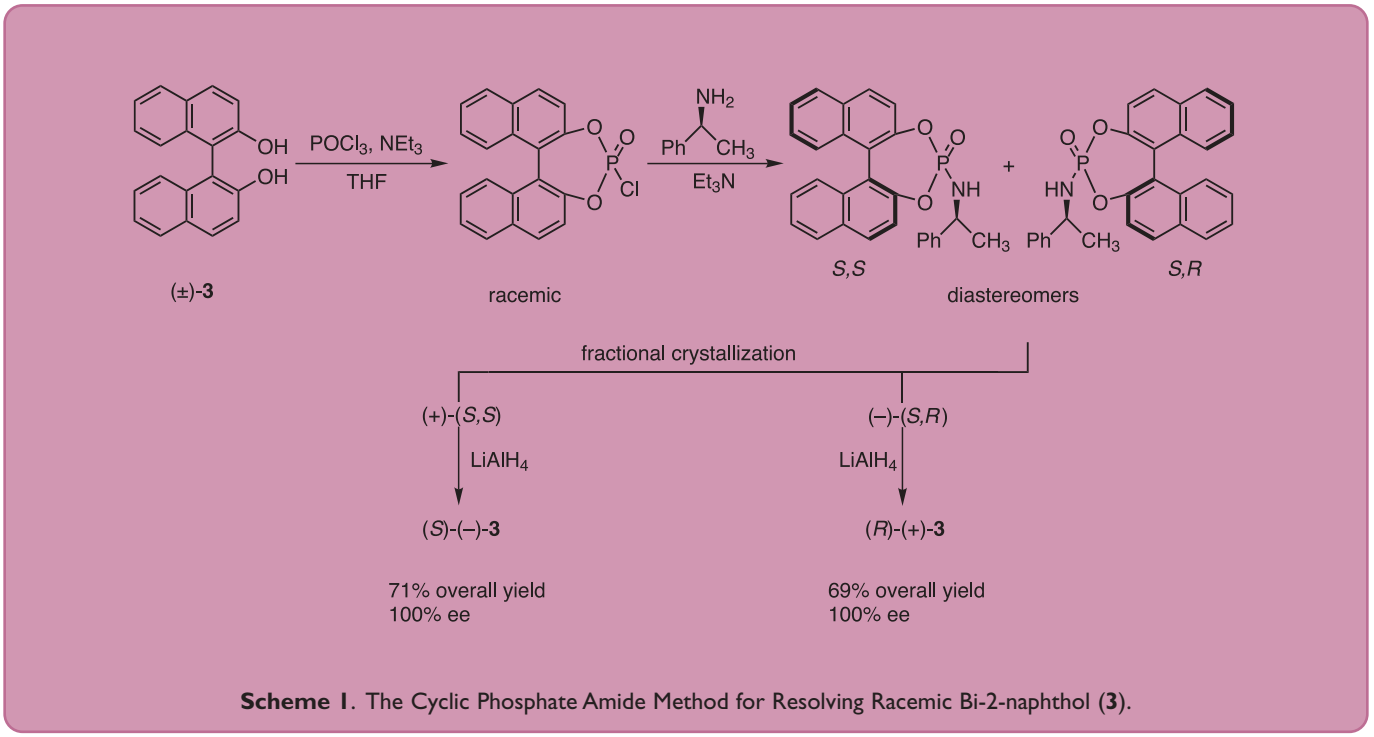
Even though asymmetric syntheses of bi-2-naphthol (**3**) have been reported,[5] this important chiral material and its substituted derivatives are generally obtained in enantiomerically pure forms by resolution of the racemic mixtures.[4] Racemic bi-2-naphthol can be readily prepared by Cu(II)-catalyzed oxidative coupling of 2-naphthol in the presence of air (**eq 1**).[5m]

Of the various resolution methods that have been reported for **3**, procedures involving the preparation of the corresponding racemic phosphoric acid derivatives have been widely utilized.[6] In the original procedure, the racemic cyclic binaphthyl phosphate was resolved via its cinchonine salt.[6] Later on, procedures were reported for the preparation of diastereomeric phosphate esters of chiral menthol,[7] or phosphate amides of commercially available chiral α-methylbenzylamine[8] (**Scheme 1**).

These methods can be readily adapted to large-scale synthesis. For example, the cyclic phosphate procedure has been utilized by Cram and coworkers on a molar scale to obtain chiral bi-2-naphthols for use in their studies of chiral host–guest complexes.[9] Several substituted bi-2-naphthols have also been resolved via the preparation of similar cyclic phosphate esters.[4] However, one drawback of this procedure is its use of $LiAlH_4$ to cleave the phosphate salts, amides, or esters, since $LiAlH_4$ is somewhat expensive and requires special handling. Accordingly, the search for more convenient procedures for the resolution of bi-2-naphthol is continuing.







Scheme 1. The Cyclic Phosphate Amide Method for Resolving Racemic Bi-2-naphthol (**3**).

2.1.2. Through Selective Enzymatic Hydrolysis of the Corresponding Esters

The enzymatic resolution of racemic alcohols through partial hydrolysis of the corresponding esters is one of the more widely applied methods for obtaining enantiomerically pure alcohols. Detailed studies on the resolution of racemic bi-2-naphthol esters have been reported, and a large-scale (0.7 mole) procedure has been described (**Scheme 2**).[10] This approach has also proven useful for resolving the corresponding octahydrobi-2-naphthol (**5**) and spirobiindanol **6**.[10]

Enantiomerically pure 1,2-cyclohexanediols have similarly been prepared by the enzymatic resolution of the corresponding diacetate **7** (**eq 2**).[11]

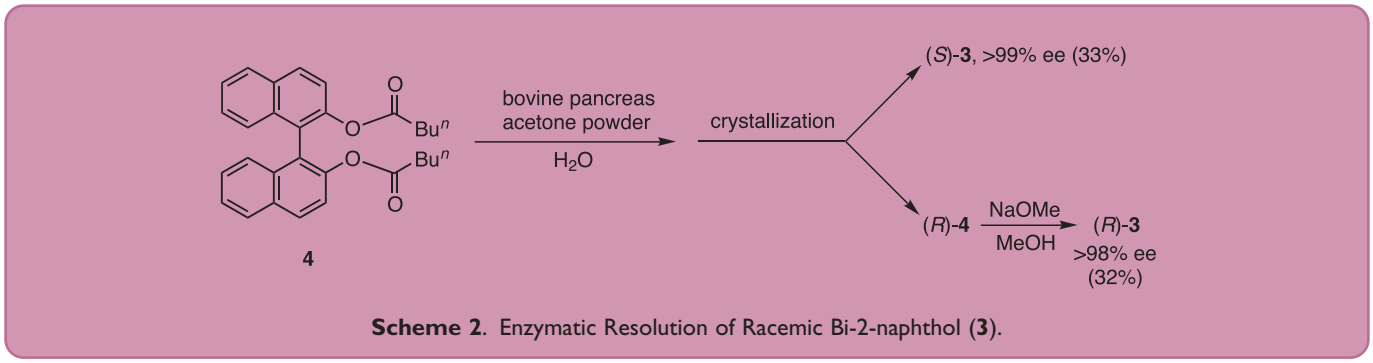
2.1.3. Via Diastereomeric Inclusion Complexes with Chiral Tartaric Acid Amides

Chiral host amides **9**, **10**, and **11**—which are derived from inexpensive, naturally occurring (*R*,*R*)-(+)-tartaric acid—form diastereomeric 1:1 inclusion complexes with guests bi-2-naphthol (**3**), 10,10'-dihydroxy-9,9'-biphenanthryl (**12**), and 2,2'-dihydroxy-9,9'-spirobifluorene (**13**), respectively.[12] Such complexes were utilized for the resolution of racemic **3** (**Scheme 3**) and racemic **12** (**Scheme 4**).[12]

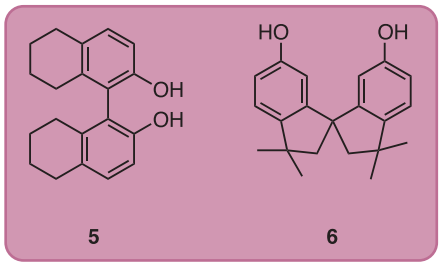
A diastereomeric 1:1 inclusion complex of diol **13** and amide **11** was similarly prepared in ethanol, crystallized from the same solvent, decomposed with dilute sodium hydroxide, and acidified with dilute hydrochloric acid to give (+)-**13** in 90% yield and >99% ee.[12]

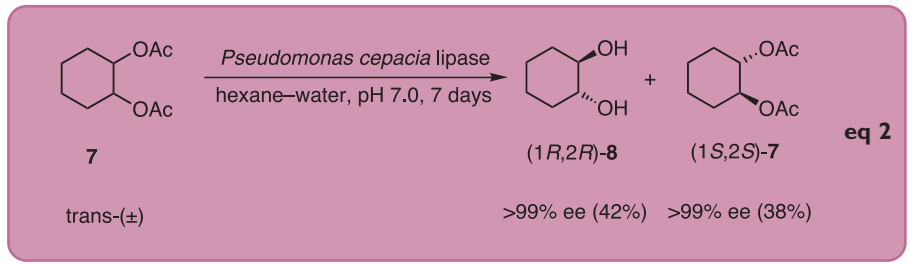
2.1.4. Via Diastereomeric Inclusion Complexes with Chiral Cinchonidium Halides

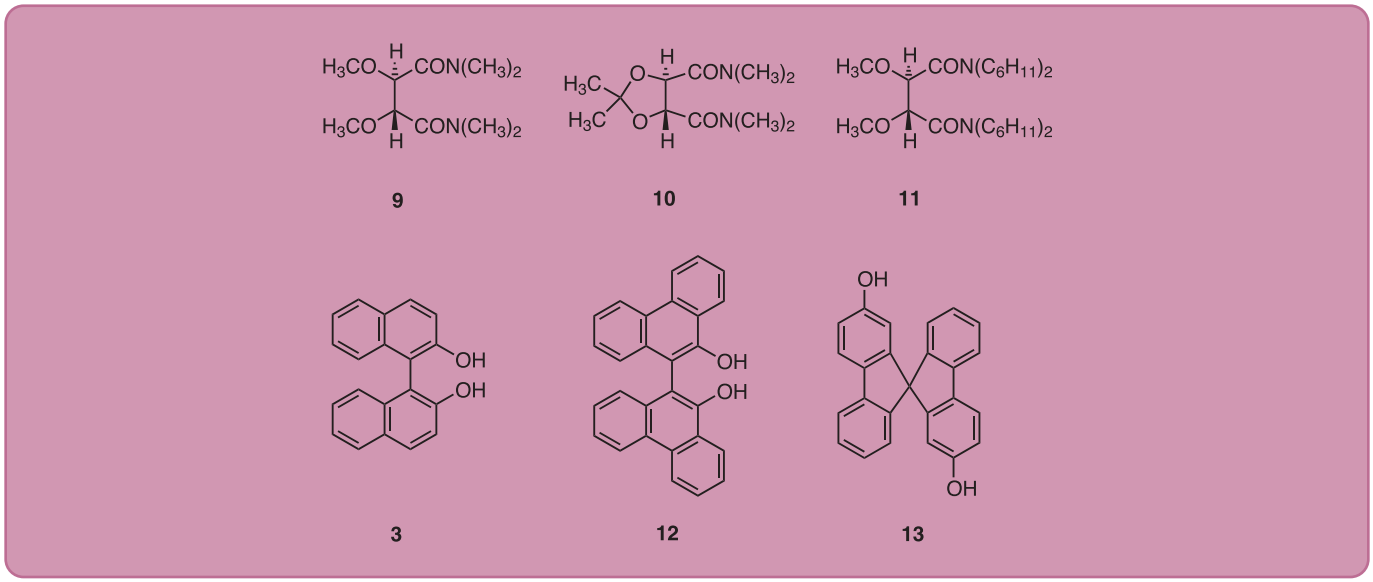
Inclusion complexes of bi-2-naphthol (**3**) with chiral *N*-benzylcinchonidium chloride (**14**) have been exploited in the resolution of



Scheme 2. Enzymatic Resolution of Racemic Bi-2-naphthol (**3**).







racemic **3** (**Scheme 5**).[13] (*R*)-**12** (>99% ee, 40% yield) and (*S*)-**12** (>58% ee, 60% yield) were similarly obtained from racemic **12** by employing *N*-butyl cinchonidium bromide (**15**) in methanol.[13] A slight modification of this procedure—using **14**, acetonitrile as solvent, and EtOAc/1N HCl to cleave the complex—afforded both enantiomers of **3** in ≥99% ee.[14]

2.1.5. With Chiral Diamines

Chiral 1,2-diaminocyclohexane (**16**) forms diastereomeric complexes with bi-2-naphthol (**3**).[15] Such derivatives were readily separated and crystallized to obtain both enantiomers of **3** in high enantiomeric purity (**Scheme 6**).[15]

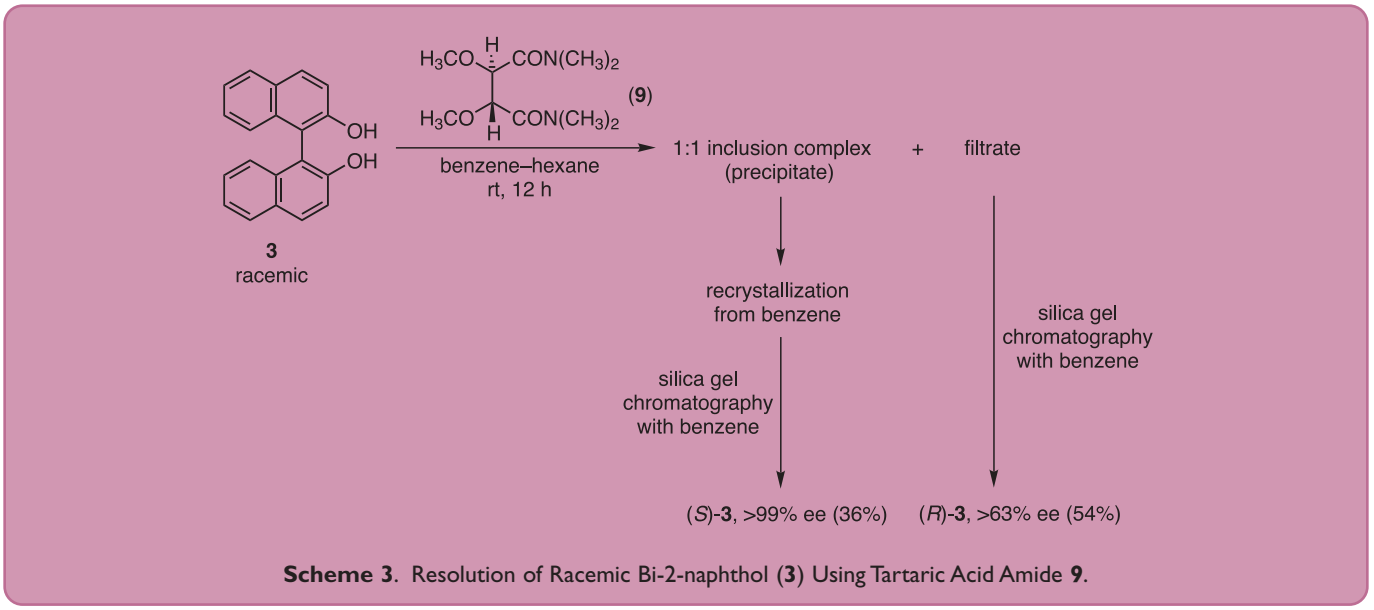
Similar results were obtained with chiral 1,2-diphenyl-1,2-diaminoethane.[12] Upon heating the mixture of diastereomeric complexes prepared from racemic **3** and the chiral amine, enantiomerically pure samples of **3** were obtained in 154–160% of the theoretical yields via a novel epimerization–crystallization process.[15]

2.1.6. With (S)-Proline

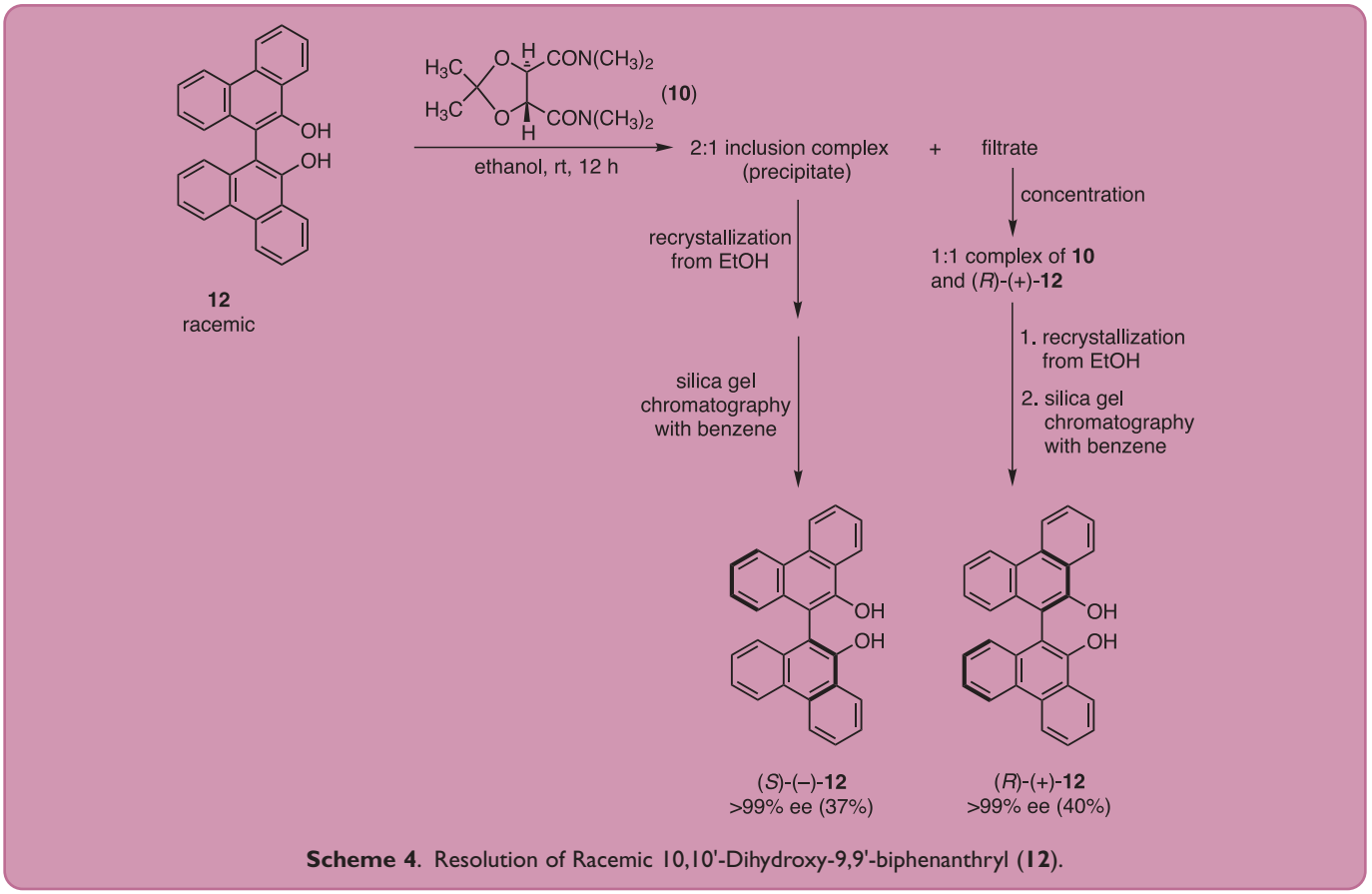
The cyclic phosphate derivatives of bi-2-naphthol (**3**) (Scheme 1) are hydrolytically stable, and hence require $LiAlH_4$ to regenerate **3**. In contrast, the corresponding diastereomeric borate complexes **17–20**, which are expected to be crystalline, should undergo hydrolysis readily. Such diastereomeric derivatives should also be easy to prepare from boric acid and amino acids, amino alcohols, or amines.

Hence, such a method would, in principle, be useful for the resolution of diols, amino acids, amino alcohols, and amines. Accordingly, systematic studies were undertaken to develop synthetic methods for such borate complexes using inexpensive boric acid, $B(OH)_3$.[16] The reaction of boric acid, bi-2-naphthol (**3**), and (*S*)-proline (**21**) did not give the corresponding borate derivative, **22**, as a major product. Instead, a 2:1 complex, **23**, of **3** and **21** formed under these conditions.[16,17] The partially resolved **3** was readily obtained by hydrolysis of **23** (**Scheme 7**).[17]

Complex **23** is also formed in other solvents such as methanol, dichloromethane,



Scheme 3. Resolution of Racemic Bi-2-naphthol (**3**) Using Tartaric Acid Amide **9**.



Scheme 4. Resolution of Racemic 10,10'-Dihydroxy-9,9'-biphenanthryl (**12**).

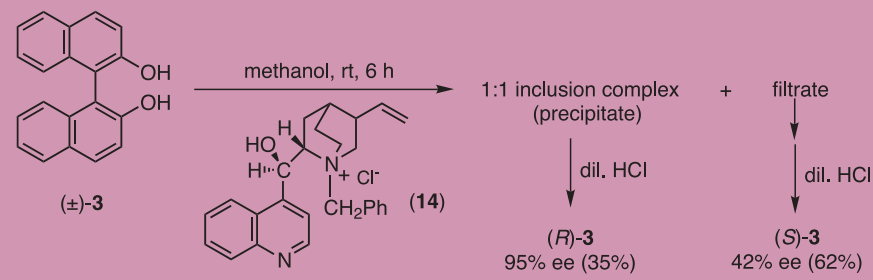
and acetonitrile.[18] The crystalline complex obtained in methanol has been characterized by X-ray crystallographic analysis. Samples of >99% ee are readily obtainable by repetition of the procedure starting from nonracemic **3**.[18]

Racemic diol **24**, and dicarboxylic acids **25** and **26** were also resolved via the corresponding diastereomeric complexes with (*S*)-proline, but without using boric acid.[19,20]

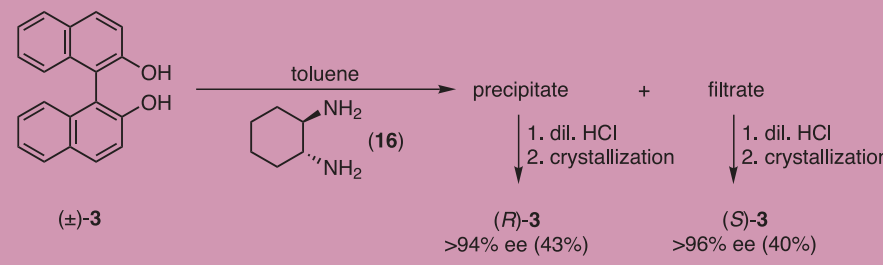
2.1.7. Via Diastereomeric Borate Complexes

An interesting procedure for the purification of nonracemic samples of **3** was devised by using boric acid and taking advantage of the predominant formation of homochiral complexes **19** or **20** (**Scheme 8**).[17,18]

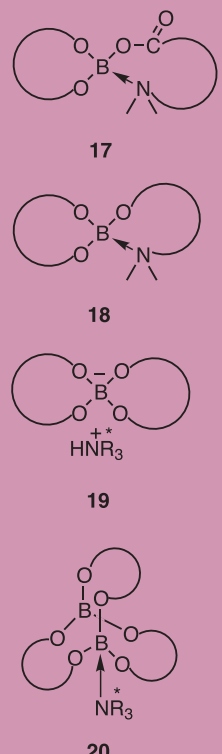
Subsequently, a simple and convenient procedure was developed for the resolution of racemic **3** by employing boric acid and (*R*)-(+)-α-methylbenzylamine (**Scheme 9**).[21] The intermediate borate complex of type **19** was characterized by single-crystal X-ray analysis.

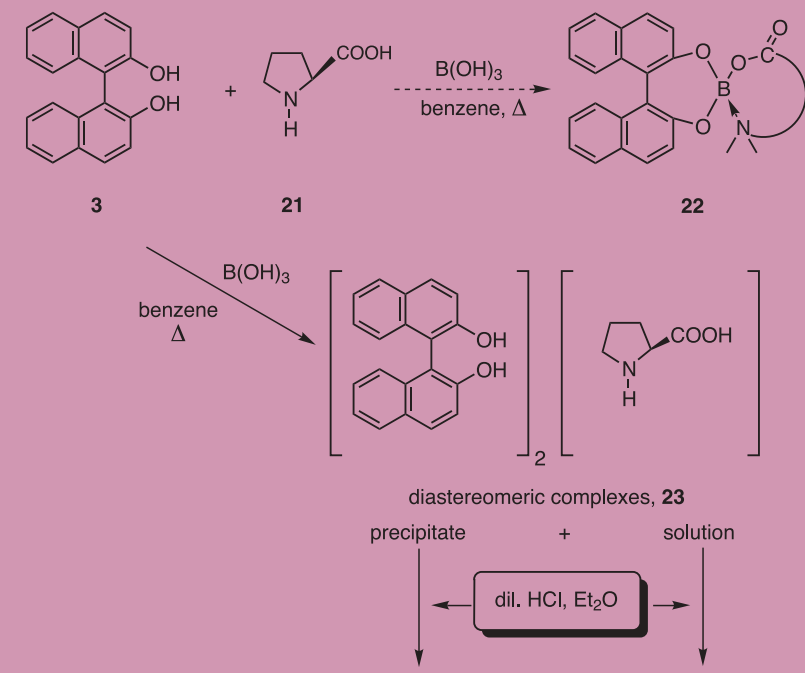


Scheme 5. Resolution of Bi-2-naphthol (**3**) with Chiral *N*-Benzylcinchonidium Chloride (**14**) in Methanol.



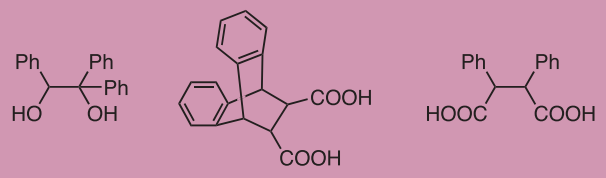
Scheme 6. Resolution of Racemic Bi-2-naphthol (**3**) with Chiral 1,2-Diaminocyclohexane (**16**).



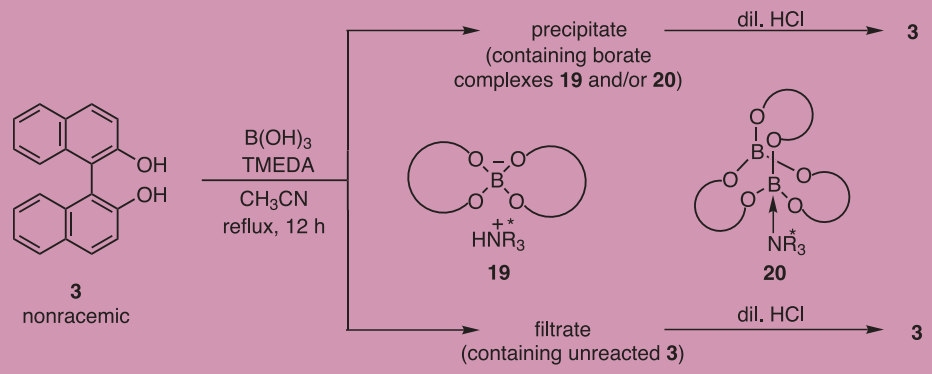


starting mat. (**3**)		**3** from precipitate			**3** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R+*S*	00	*S*	65	43	*R*	44	51
S	10	*S*	64	65	*R*	70	25
S	87	*S*	>99	77	*S*	35	11
R	44	*R*	90	45	*R*	06	41
R	90	*R*	>98	70	*R*	28	18

Scheme 7. Resolution of Racemic Bi-2-naphthol (**3**) with (*S*)-Proline (**21**).

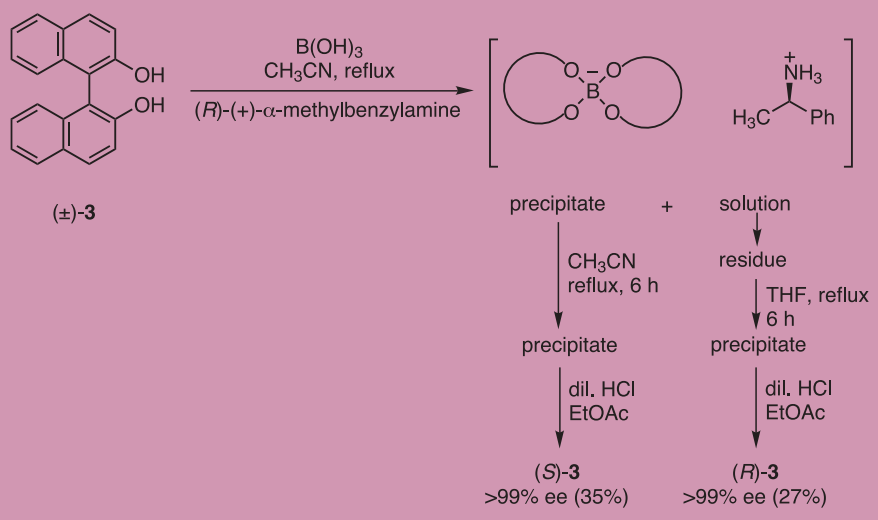


24 **25** **26**



starting mat. (**3**)		$B(OH)_3$	**3** from precipitate			**3** from filtrate		
config.	ee, %	(mmol)	config.	ee, %	yield, %	config.	ee, %	yield, %
R	17	0.57	*R*	88	11	*R*	03	76
R	34	1.14	*R*	92	31	*S*	05	55
R	79	2.67	*R*	93	77	*S*	06	10
S	18	0.60	*S*	89	13	*S*	05	75
S	34	1.10	*S*	95	28	*S*	01	54
S	75	2.50	*S*	95	77	*R*+*S*	00	10

Scheme 8. Purification of Nonracemic Bi-2-naphthol (**3**) Using Boric Acid.



Scheme 9. Resolution of Bi-2-naphthol (**3**) Using Boric Acid and Chiral α-Methylbenzylamine.

As discussed in Section 2.1.6, attempts at effecting the resolution of **3** using amino acids and amino alcohols, and through the intermediacy of borate complexes of type **17–20**, resulted in the discovery that **3** forms diastereomeric complexes with (*S*)-proline. Later on, such borate complexes were successfully prepared using borane and quinine; however, the structure of the borate–quinine complex was not established unambiguously (**Scheme 10**).[22]

The resolution can also be carried out via the corresponding "BOB"complexes and reaction of these with (*S*)-proline (**Scheme 11**).[23] Again, the structure of the complex formed under these conditions was not examined by X-ray analysis.

2.2. Resolution of Racemic 1,2- and 1,4-Diols Using Boric Acid and (S)-Proline

Racemic 1,2-diphenylethanediol (**29**) and 2,3-diphenyl-1,4-butanediol (**30**) were readily resolved via diastereomeric borate complexes using boric acid and (*S*)-proline (**Scheme 12**).[19] ^{1}H NMR studies provided support for the formation of the diastereomeric complex of type **17**.

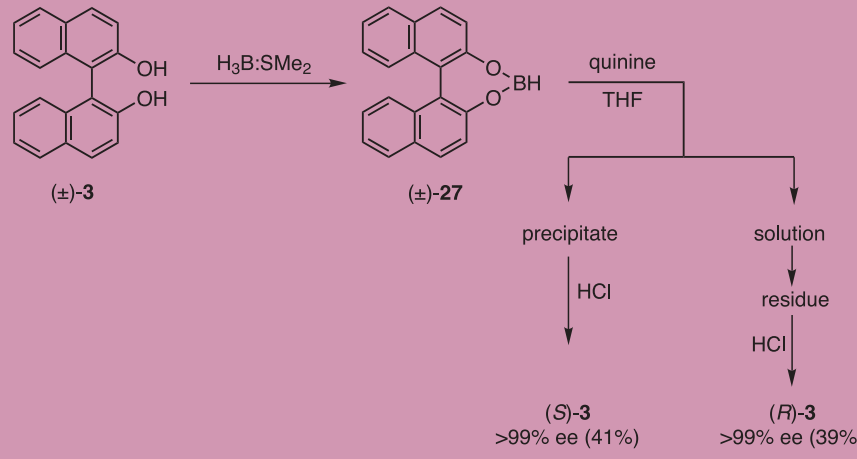
Racemic **30** is accessible by the $TiCl_4/Et_3N$ induced coupling of ethyl phenylacetate, followed by hydrolysis and reduction with borane (**Scheme 13**).[24]

3. Racemic Amino Alcohols

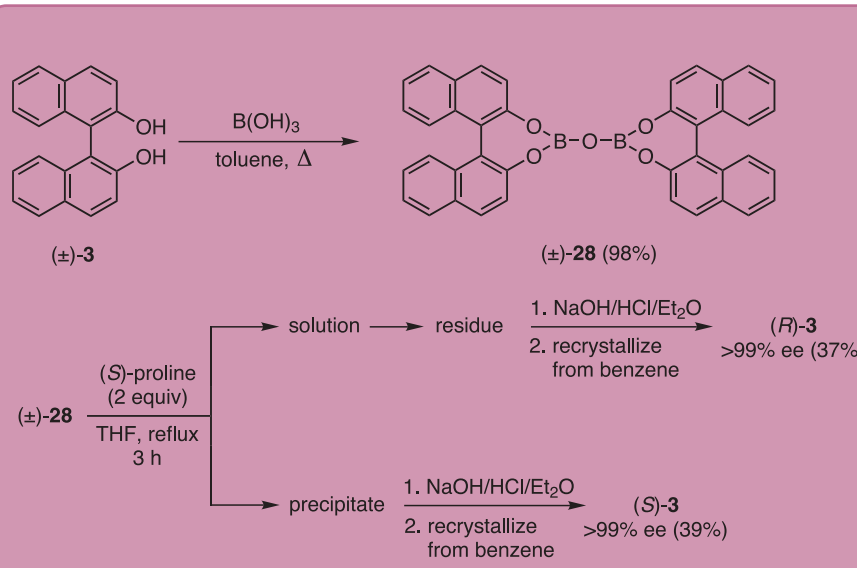
3.1. Resolution of Diphenylprolinol with Chiral Bi-2-naphthol and Boric Acid

Since chiral bi-2-naphthol became accessible, systematic investigations were undertaken to synthesize and resolve amino alcohols and derivatives, which were expected to form borate complexes of type **17–20** with chiral bi-2-naphthol and boric acid. The widely used diphenylprolinol (**1**) and other readily accessible amino alcohols were chosen for these studies. (*S*)-Diphenylprolinol [DPP, (*S*)-**1**] had been prepared by the addition of phenylmagnesium bromide to the N-protected (*S*)-proline ester.[25] Our preparation of (*S*)-**1** for application in large-scale synthesis was a slight modification and an improvement of the reported procedure (**Scheme 14**).[26]

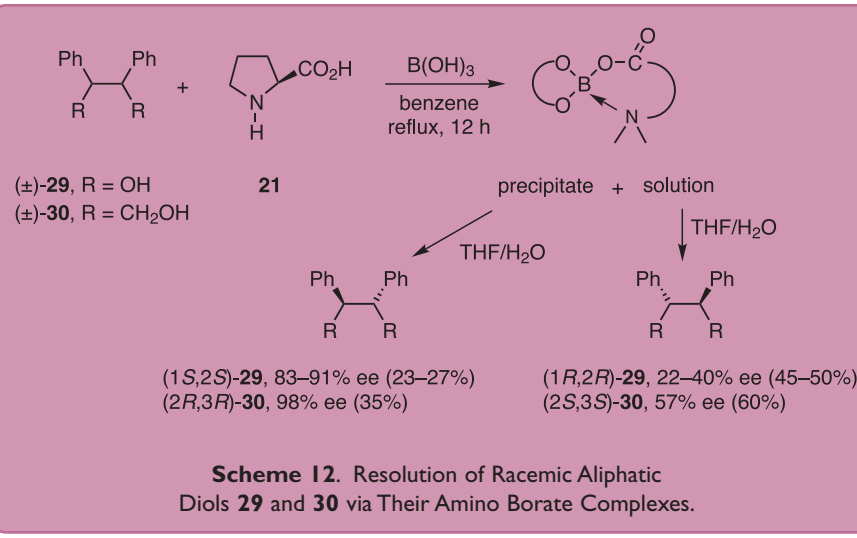
(*S*)-Diphenylprolinol is the precursor of the useful CBS oxazaborolidine catalyst that is utilized in the asymmetric borate reduction of ketones.[1] Accordingly, it was of interest to synthesize the enantiopode, (*R*)-diphenylprolinol, for applications in such oxazaborolidine reductions.[25] Since (*R*)-proline and racemic proline are somewhat



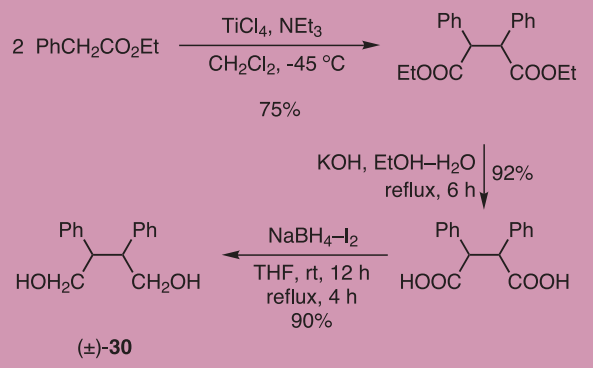
Scheme 10. Resolution of Bi-2-naphthol (**3**) Using Borane and Chiral Quinine.



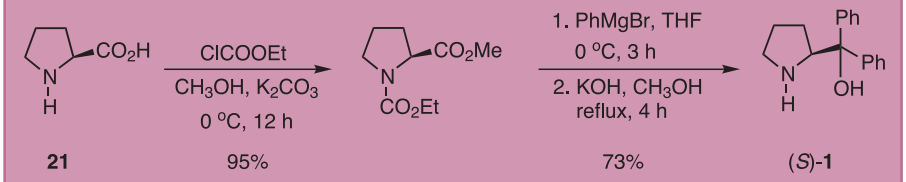
Scheme 11. Resolution of Bi-2-naphthol (**3**) through a "BOB" Complex.



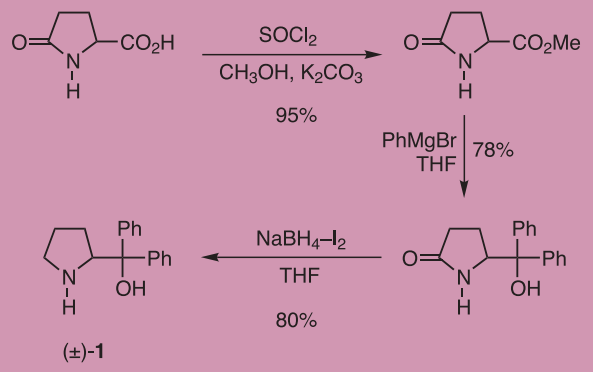
Scheme 12. Resolution of Racemic Aliphatic Diols **29** and **30** via Their Amino Borate Complexes.



Scheme 13. Preparation of Racemic 2,3-Diphenyl-1,4-butanediol (**30**).



Scheme 14. Synthesis of (*S*)-Diphenylprolinol.



Scheme 15. Alternative New Synthesis of Racemic Diphenylprolinol.

expensive, an alternative route had been developed by Corey and co-workers for the preparation of racemic diphenylprolinol starting from pyroglutamic acid.[25] The resulting racemic **1** was resolved using (*S*)-(+)- and (*R*)-(–)-*O*-acetylmandelic acids.[25b] We have reported an alternative new procedure for the synthesis of racemic diphenylprolinol, which employs a $NaBH_4$–I_2 reduction in a crucial step of the synthesis (**Scheme 15**).[27]

Racemic diphenylprolinol prepared in this way was resolved following the chiral bi-2-naphtholborate methodology (**Scheme 16**).[27] The intermediate borate complex was characterized by single-crystal X-ray analysis.

3.2. Resolution of Amino Alcohols Prepared from Cyclohexene Oxides

Racemic amino alcohols can be readily prepared through ring-opening of epoxides. For example, trans racemic amino alcohol **31** is obtained by heating cyclohexene oxide with pyrrolidine.[27,28] Racemic amino alcohol **31** formed borate complexes of type **19** with boric acid and bi-2-naphthol (**3**) in THF or acetonitrile. After a simple dilute hydrochloric acid workup of the precipitate and filtrate fractions, the nonracemic amino alcohol samples were obtained and were further purified by repetition of the procedure (**Scheme 17**).

The corresponding OMe derivative, **32**, gave better results: *trans*-(±)-**32** led with (*R*)-**3** to (1*R*,2*R*)-**32** (>44% ee, 63% yield) and (1*S*,2*S*)-**32** (83% ee, 30% yield).[27,28] The borate complex obtained in this case was crystalline, and the configurational assignments were confirmed by X-ray crystal-structure analysis.

3.3. Purification of Diastereomeric Amino Alcohols Obtained from Meyers' Lactam

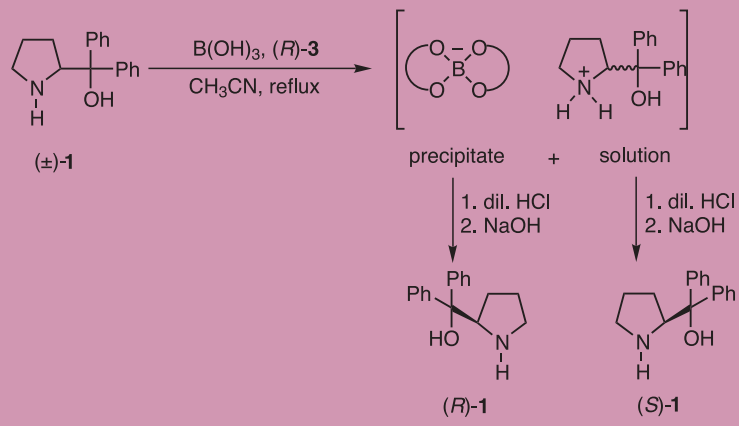
Nonracemic diastereomeric amino alcohol **34** is readily accessed by synthesis and cleavage of Meyers' lactam (**33**) (**Scheme 18**).[27] Diastereomeric amino alcohol **34**, prepared in this way, was purified using bi-2-naphthol (**3**) and boric acid (**Scheme 19**).[27] The intermediate borate complex was characterized by single-crystal X-ray analysis.

3.4. Resolution of Amino Alcohols with Chiral Bi-2-naphthyl-phosphoric Acid

Racemic amines are generally resolved using chiral resolving agents such as camphor-10-sulphonic acid, tartaric acid and its derivatives, and mandelic acid. Chiral bi-2-naphthylphosphoric acid—accessible through reaction of chiral bi-2-naphthol (**3**) with $POCl_3$ (Scheme 1)—is a promising resolving agent for racemic amino alcohols. For example, racemic diphenylpiperidinol (**35**) was resolved using (*S*)-(–)-bi-2-naphthylphosphoric acid [(*S*)-**36**] (**Scheme 20**).[6]

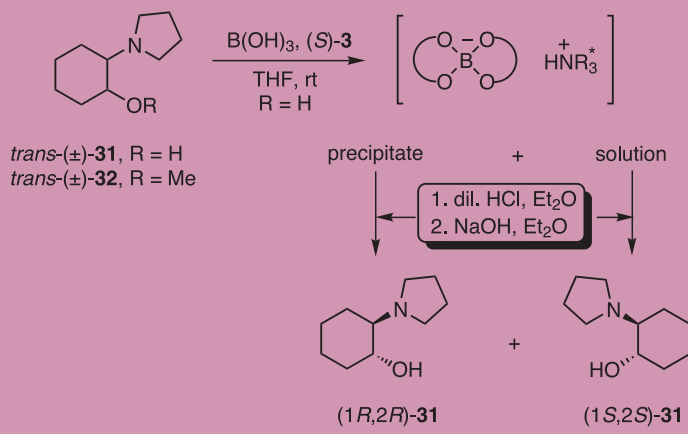
3.5. Resolution of Amino Alcohols Prepared by the Reduction of Oximes of α-Keto Esters

The $NaBH_4$–I_2 reduction of naturally occurring chiral amino acids **37** yields the corresponding *S* amino alcohols **38** (**eq 3**).[29] The corresponding racemic amino alcohols, **39**, are available by reduction of the oximes of α-keto esters with $NaBH_4$–I_2 (**eq 4**).[30] These amino alcohols form diastereomeric complexes with dibenzoyl-L-tartaric acid (**40**).[30] Nonracemic mixtures of the amino alcohols are obtained through precipitation of the complexes in acetone. The resolutions of phenylglycinol (**39a**) and phenylalaninol (**39b**) have been studied in detail. Interestingly, the nature of the nonracemic material obtained depends on the amount of resolving agent used. Thus, phenylglycinol samples of >90% ee are obtained by adding the resolving agent in portions (**Scheme 21**).[30] The nonracemic amino alcohols obtained in this way are readily purified further through crystallization using achiral dicarboxylic acids such as oxalic acid (**Scheme 22**).[30]



starting mixt. (**1**)		**1** from precipitate			**1** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R+*S*	0	*R*	90	18	*S*	20	80
R	42	*R*	>99	28	*S*	25	69
R	90	*R*	>99	78	*S*	30	20

Scheme 16. Resolution of Racemic Diphenylprolinol Using Boric Acid and Chiral Bi-2-naphthol.



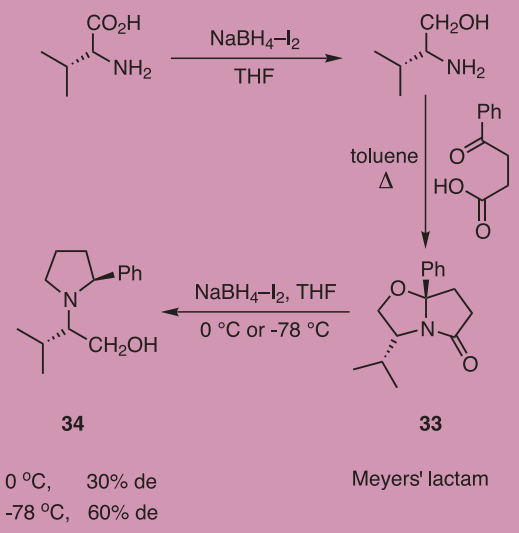
starting mixt. (**31**)		**31** from precipitate			**31** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
racemic	0	1*R*,2*R*	38	40	1*S*,2*S*	36	45
1*R*,2*R*	38	1*R*,2*R*	79	40	1*R*,2*R*	11	55
1*R*,2*R*	79	1*R*,2*R*	>99	35	1*R*,2*R*	08	50

Scheme 17. Resolution of Racemic Amino Alcohol **31**.

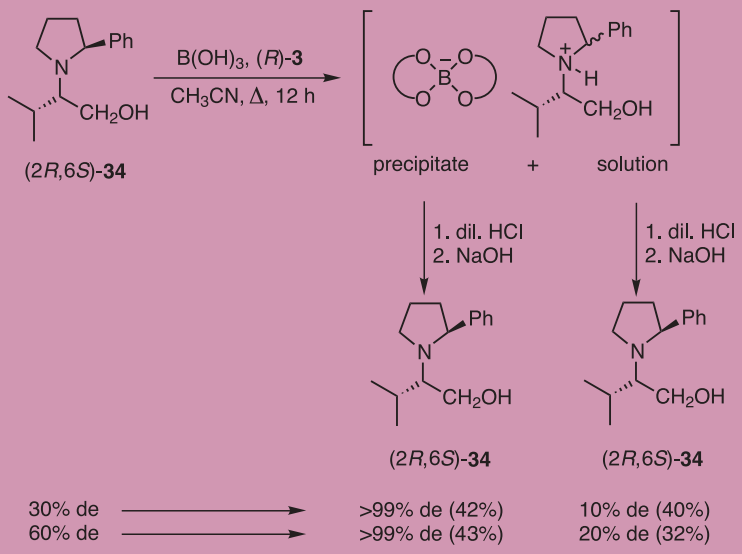
Nonracemic mixtures of phenylalaninol (**39b**) gave better results in the purification sequence that employs oxalic acid (**Scheme 23**).[30] Presumably, the oxalic acid forms predominantly homochiral aggregates, resulting in the precipitation of the complex enriched in the predominant isomer. X-ray crystal-structure analysis of the complexes is necessary for further understanding of the nature of the aggregates formed in these resolution processes.

4. Conclusions

Chiral diols and amino alcohols are widely used in asymmetric transformations both as building blocks and ligands for the preparation of catalysts. Although asymmetric syntheses are preferred for obtaining these compounds in enantiomerically pure forms, resolution methods of racemic or enriched mixtures, especially to attain both enantiomers, could become good alternatives, if they could be adapted to large scale. Resolution procedures involving the use of well-known resolving agents such as chiral camphor-10-sulphonic acid, tartaric acid, and mandelic acid have been available for a long time. New resolution methods that rely on enzymes, inclusion complexes, and phosphate and borate complexes would further expand the scope of the resolution approach. Novel methods for the purification of diols and amino alcohols using achiral reagents further illustrate the applicability of



Scheme 18. Synthesis of Diastereomeric Amino Alcohol **34**.



Scheme 19. Purification of Amino Alcohol **34** by Employing Boric Acid and Chiral Bi-2-naphthol.

this approach to the isolation of enantiopure organic compounds. Such a purification of partially resolved materials would involve selective formation of homochiral complexes and, hence, has relevance to nonlinear effects (i.e., a ligand with lower ee leading to a product with a higher ee) in asymmetric synthesis.[31] Accordingly, such concepts should further stimulate research in the exciting area of asymmetric synthesis.

5. Acknowledgement

The author is thankful to his students, whose names appear in the references, for their contributions to this research program. Financial support for this research program from the Department of Science and Technology, Government of India, is gratefully acknowledged.

6. References and Notes

(1) For a recent review on the applications of diphenylprolinol and diphenylamino alcohols in oxazaborolidine-catalyzed reductions, see Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.

(2) For asymmetric syntheses using 1,2-amino alcohols, see (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(3) For a review on the synthesis and applications of TADDOL derivatives, see Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 92.

(4) For a review on the synthesis and applications of bi-2-naphthol derivatives, see Pu, L. *Chem. Rev.* **1998**, *98*, 2405.

(5) For asymmetric syntheses of bi-2-naphthols, see (a) Feringa, B.; Wynberg, H. *Tetrahedron Lett.* **1977**, 4447. (b) Feringa, B.; Wynberg, H. *Bioorg. Chem.* **1978**, *7*, 397. (c) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261. (d) Yamamoto, K.; Fukushima, H.; Nakazaki, M. *J. Chem. Soc., Chem Commun.* **1984**, 1490. (e) Brussee, J.; Groenendijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313. (f) Yamamoto,

K.; Fukushima, H.; Yumioka, H.; Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3633. (g) Smrcina, M.; Lorenc, M.; Hanus, V.; Sedmera, P.; Kocovsky, P. *J. Org. Chem.* **1992**, *57*, 1917. (h) Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534. (i) Hamada, T.; Ishida, H.; Usui, S.; Watanabe, Y.; Tsumura, K.; Ohkubo, K. *J. Chem. Soc., Chem. Commun.* **1993**, 909. (j) Osa, T.; Kashiwagi, Y.; Yanagisawa, Y.; Bobbitt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2535. (k) Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983. (l) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S. *Tetrahedron Lett.* **1995**, *36*, 9519. (m) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-i.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264.

(6) Jacques, J.; Fouquey, C.; Viterbo, R. *Tetrahedron Lett.* **1971**, 4617.

(7) Brunel, J.-M.; Buono, G. *J. Org. Chem.* **1993**, *58*, 7313.

(8) Gong, B.-g.; Chen, W.-y.; Hu, B.-f. *J. Org. Chem*. **1991**, *56*, 423.

(9) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173.

(10) Kazlauskas, R. J. *J. Am. Chem. Soc*. **1989**, *111*, 4953.

(11) Caron, G.; Kazlauskas, R. J. *J. Org. Chem.* **1991**, *56*, 7251.

(12) Toda, F.; Tanaka, K. *J. Org. Chem.* **1988**, *53*, 3607.

(13) (a) Tanaka, K.; Okada, T.; Toda, F. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1147. (b) Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I. *J. Org. Chem*. **1994**, *59*, 5748.

(14) (a) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991. (b) For another modification involving resolution by exploiting the nature of the crystals formed, see Hu, Q.-S.; Vitharana, D.; Pu, L. *Tetrahedron: Asymmetry* **1995**, *6*, 2123.

(15) (a) Kawashima, M.; Hirayama, A. *Chem. Lett*. **1990**, 2299. (b) Kawashima, M.; Hirata, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2002.

(16) Periasamy, M. *Pure Appl. Chem.* **1996**, *68*, 663.

(17) Periasamy, M.; Prasad, A. S. B.; Kanth, J. V. B.; Reddy, C. K. *Tetrahedron: Asymmetry* **1995**, *6*, 341.

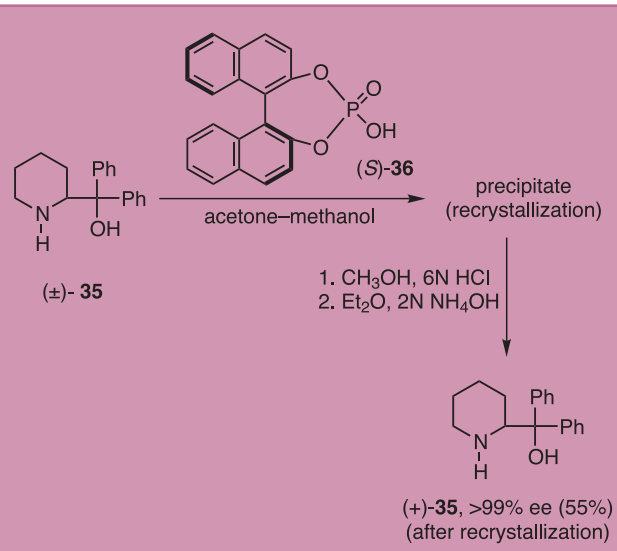
(18) (a) Periasamy, M.; Venkatraman, L.; Thomas, K. R. J. *J. Org. Chem.* **1997**, *62*, 4302. (b) Venkatraman, L.; Periasamy, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2471.

(19) (a) Periasamy, M.; Ramanathan, C. R.; Prasad, A. S. B.; Kanth, J. V. B. *Enantiomer* **1998**, *3*, 3. (b) Periasamy, M.; Rao, V. D.; Seenivasaperumal, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1887.

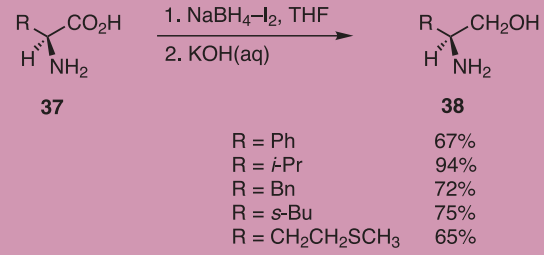
(20) Ramanathan, C. R.; Periasamy, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2651.

(21) Periasamy, M.; Venkatraman, L.; Sivakumar, S.; Sampathkumar, N.; Ramanathan, C. R. *J. Org. Chem.* **1999**, *64*, 7643.

(22) Shan, Z.; Wang, G.; Duan, B.; Zhao, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2847.



Scheme 20. Resolution of Racemic Amino Alcohol **35** with Chiral Bi-2-naphthylphosphoric Acid.



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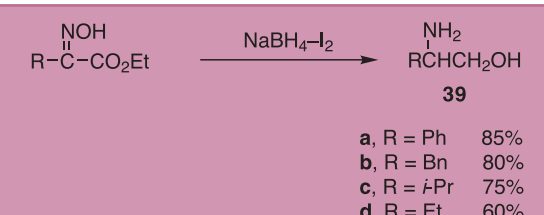


eq 4

(23) Shan, Z.; Xiong, Y.; Li, W.; Zhao, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3985.

(24) (a) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem*. **1996**, *61*, 2809. (b) Rao, V. D.; Periasamy, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1151. (c) Rao, V. D.; Periasamy, M. *Synthesis* **2000**, 703.

(25) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc*. **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc*. **1987**, *109*, 7925.

(26) (a) Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127. (b) Periasamy, M.; Kanth, J. V. B.; Prasad, A. S. B. *Tetrahedron* **1994**, *50*, 6411. (c) Kanth, J.V.B. Ph.D. Thesis, University of Hyderabad, Hyderabad, India, 1993; p 76.

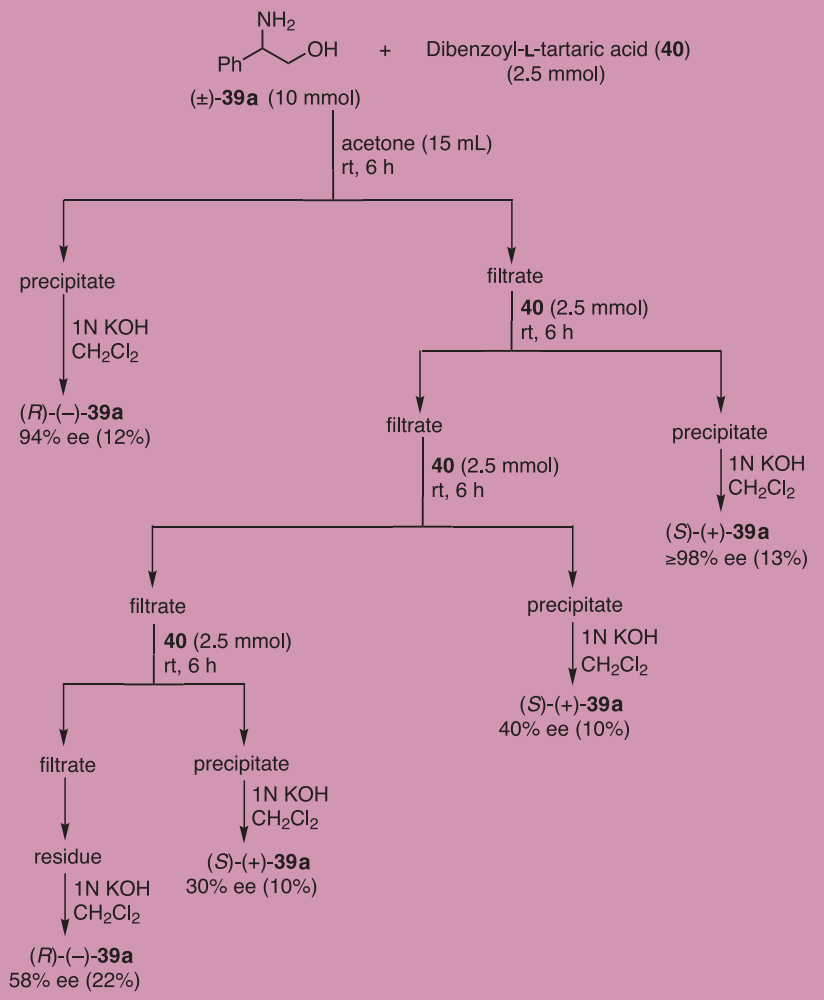
(27) (a) Periasamy, M.; Sampathkumar, N.; Sivakumar, S.; Rao, V. D.; Ramanathan, C. R.; Venkatraman, L. *J. Org. Chem.* **2001**, *66*, 3828. (b) Sivakumar, S. Ph.D. Thesis, University of Hyderabad, Hyderabad, India, 2002; pp 69–71.

(28) Periasamy, M.; Ramanathan, C. R.; Sampathkumar, N. *Tetrahedron:Asymmetry* **1999**, *10*, 2307.

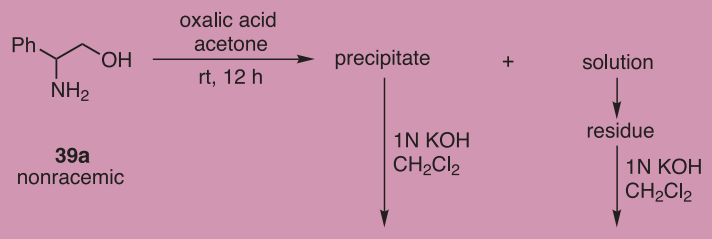
(29) (a) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568. (b) Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964. (c) Prasad, A. S. B.; Kanth, J.V.B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.

(30) Periasamy, M.; Sivakumar, S.; Narsireddy, M. University of Hyderabad, Hyderabad, India. Unpublished work, 2002.

(31) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2922.



Scheme 21. Resolution of Racemic Phenylglycinol (**39a**) with Dibenzoyl-L-tartaric Acid (**40**).

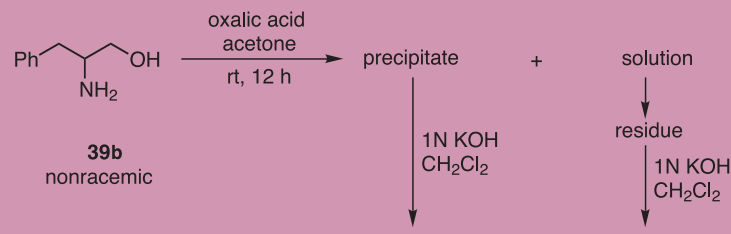


starting mixt. (**39a**)		**39a** from precipitate			**39a** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R	15	*R*	30	11	*R*	06	76
R	30	*R*	50	31	*R*	05	55
R	50	*R*	70	48	*S*	06	45
R	70	*R*	90	48	*S*	06	45
R	90	*R*	98	48	*S*	06	45

Scheme 22. Purification of Nonracemic Phenylglycinol (**39a**) Using Oxalic Acid.

About the Author

Mariappan Periasamy was born in Srivilliputtur, Tamil Nadu State, India. In the period 1970–1975, he studied for his B.S. (Special) and M.S. degrees at the American College, Madurai, India. He obtained his Ph.D. degree from the Indian Institute of Science, Bangalore, for his research work (1975–1979) in organic chemistry under the guidance of Professor M. Vivekananda Bhatt. After postdoctoral work with Professor Herbert C. Brown at Purdue University on the nonclassical ion problem (1979–1982), he joined the faculty of the School of Chemistry, University of Hyderabad, as a lecturer in July 1982. He was promoted to reader in February 1987, and became a full professor in April 1993. He was a visiting scientist/faculty at the Laboratory of Coordination Chemistry, Toulouse, France (1995), the University of Amsterdam (1996), the University of Marburg (1997), Purdue University (1999), and the University of Paris-Sud (2000). He is a recipient of the Shanti Swarup Bhatnagar Prize for Chemical Sciences (1996) awarded by the CSIR, Government of India, and was elected a fellow of the Indian Academy of Sciences, Bangalore, in 1994. His research interests are in the areas of organometallics and chiral reagents. Very recently, he has initiated a new research program on the conversion of farm waste to chemical feedstock, with the objective of developing viable, sustainable, renewable, and environmentally benign energy sources.



starting mixt. (**39b**)		**39b** from precipitate			**39b** from solution		
config.	ee, %	config.	ee, %	yield, %	config.	ee, %	yield, %
R	17	*R*	35	11	*R*	3	76
R	34	*R*	50	31	*R*	5	55
R	50	*R*	98	48	*S*	6	45
S	18	*S*	34	13	*S*	5	75
S	34	*S*	50	28	*R*+*S*	0	54
S	50	*S*	98	45	*R*+*S*	0	45

Scheme 23. Purification of Nonracemic Phenylalaninol (**39b**) Using Oxalic Acid.

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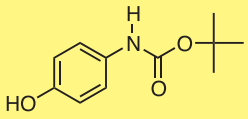
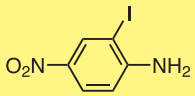
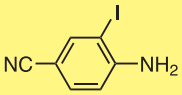
57,664-6
$C_{11}H_{15}NO_3$



57,668-9
$C_6H_5IN_2O_2$



57,801-0
$C_7H_5IN_2$



57,811-8
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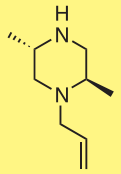
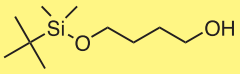
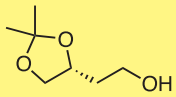


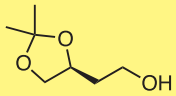
56,858-9
$C_{10}H_{24}O_2Si$



33,107-4
$C_7H_{14}O_3$



57,132-6
$C_7H_{14}O_3$



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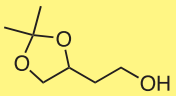
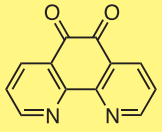
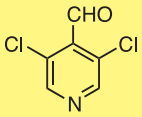
$C_7H_{14}O_3$



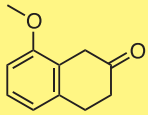
49,638-3
$C_{12}H_6N_2O_2$



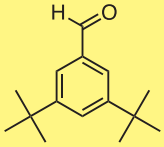
57,247-0
$C_6H_3Cl_2NO$



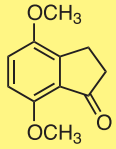
53,545-1
$C_{11}H_{12}O_2$



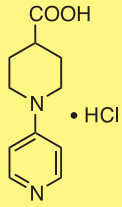
57,458-9
$C_{15}H_{22}O$



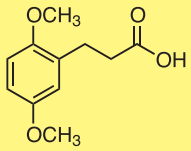
57,809-6
$C_{11}H_{12}O_3$



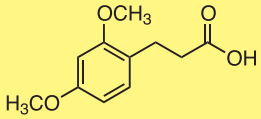
57,243-8
$C_{11}H_{14}N_2O_2 \bullet HCl$



57,565-8
$C_{11}H_{14}O_4$



57,566-6
$C_{11}H_{14}O_4$



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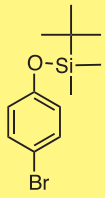
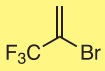
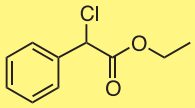
44,477-4
$C_{12}H_{19}BrOSi$



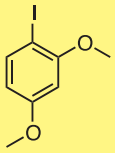
56,100-2
$C_3H_2BrF_3$



56,590-3
$C_{10}H_{11}ClO_2$



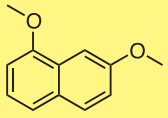
57,773-1
$C_8H_9IO_2$



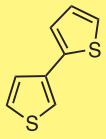
57,780-4
C_2H_2BrI

57,461-9
$C_6H_4Br_2O_2$

57,558-5
$C_{12}H_{12}O_2$



57,781-2
$C_8H_6S_2$



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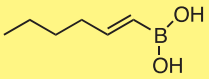
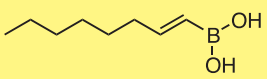
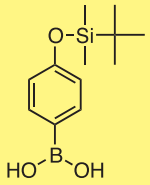
52,101-9
$C_6H_{13}BO_2$



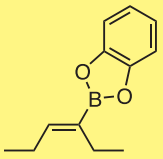
52,102-7
$C_8H_{17}BO_2$



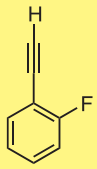
52,404-2
$C_{12}H_{21}BO_3Si$



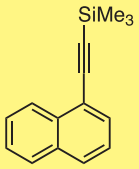
57,552-6
$C_{12}H_{15}BO_2$



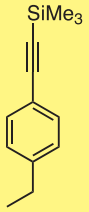
46,700-6
C_8H_5F



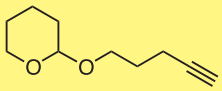
56,341-2
$C_{15}H_{16}Si$



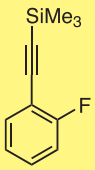
56,345-5
$C_{13}H_{18}Si$



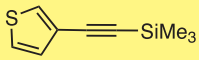
56,366-8
$C_{10}H_{16}O_2$



57,140-7
$C_{11}H_{13}FSi$

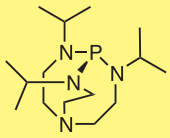


57,704-9
$C_9H_{12}SSi$

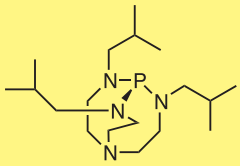


57,879-7
C_6H_4S

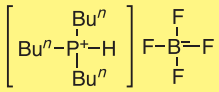
55,695-5
$C_{15}H_{33}N_4P$



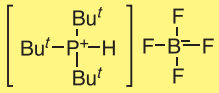
56,588-1
$C_{18}H_{39}N_4P$



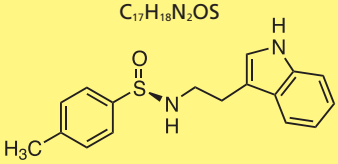
57,649-2
$C_{12}H_{28}BF_4P$



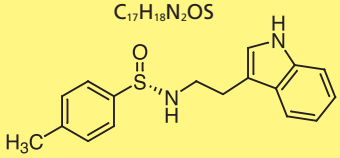
57,894-0
$C_{12}H_{28}BF_4P$



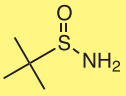
55,883-4
$C_{17}H_{18}N_2OS$



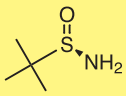
58,851-2
$C_{17}H_{18}N_2OS$



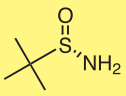
56,087-1
$C_4H_{11}NOS$



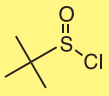
49,740-1
$C_4H_{11}NOS$



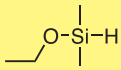
51,321-0
$C_4H_{11}NOS$



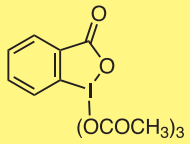
56,943-7
C_4H_9ClOS



57,863-0
$C_4H_{12}OSi$

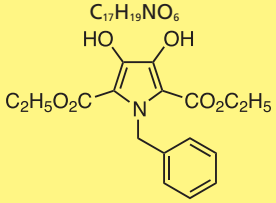


55,987-3
$C_{13}H_{13}IO_8$

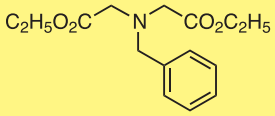


Dess–Martin Periodinane, 0.3*M* solution in dichloromethane

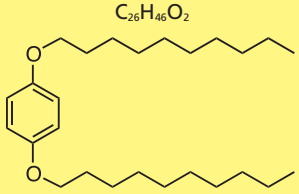
57,190-3
$C_{17}H_{19}NO_6$



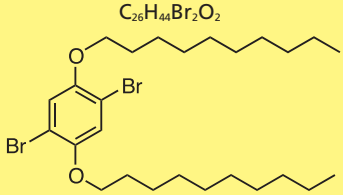
57,489-9
$C_{15}H_{21}NO_4$



57,651-4
$C_{26}H_{46}O_2$



57,837-1
$C_{26}H_{44}Br_2O_2$



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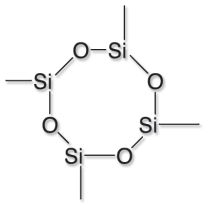
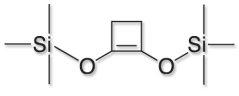
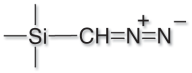


51,299-0
2,4,6,8-Tetramethylcyclotetrasiloxane, 99.5+%
CAS # 2370-88-9



29,383-0
1,2-Bis(trimethylsilyloxy)cyclobutene, 95+%
CAS # 17082-61-0



36,283-2
(Trimethylsilyl)diazomethane
2.0*M* solution in hexanes
CAS # 18107-18-1

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Our **DEAD solution, 40% in toluene (11627)** is back again! As a result of new insights into its explosive properties, recent transport legislations made this very important reagent for the Mitsunobu reaction unavailable to customers for several months. Now, Fluka is able to offer **DEAD** again in a **stable** and **safe** 40% toluene solution.

Mitsunobu reactions, i.e., the combination of an azodicarboxylate (mostly DEAD) and a phosphine (such as triphenylphosphine or tributylphosphine) are currently widely applied in C–C bond-forming reactions in organic synthesis.[1-4] Many other applications are known, such as the preparation of *N*-alkylamides or imides starting from an alcohol and amide or imide, or the condensation of a carboxylic acid and an alcohol to form the corresponding ester. Also interesting, is the inversion of configuration that takes place in the case of a chiral secondary alcohol.

11627 **Diethyl azodicarboxylate solution** (DEAD), purum, ~ 40% in toluene (^{1}H NMR)[1-4]
M_w 174.16 [1972-28-7] $C_6H_{10}N_2O_4$ 50mL; 250mL; 500mL

Other Azodicarboxylic Acid Reagents Used in the Mitsunobu Reaction:

11625 **Di-*tert*-butyl azodicarboxylate** (DBAD), purum, ≥ 98.0% (GC)
M_w 230.27 [870-50-8] $C_{10}H_{18}N_2O_4$ 5g; 25g
An acid-labile reagent that allows facile isolation of the desired products;[5] useful in electrophilic amination and hydrazination of enolates and lithium alkyls.[6-8]

11626 **Diisopropyl azodicarboxylate** (DIAD), pract., ~ 95% (GC)[1]
M_w 202.21 [2446-83-5] $C_8H_{14}N_2O_4$ 25mL; 100mL
Useful for the preparation of aryl ethers.[9]

11632 **Azodicarboxylic acid dipiperidide** (ADDP), [1,1′-(azodicarbonyl)dipiperidine], purum, ≥ 98.0% (TLC)
M_w 252.32 [10465-81-3] $C_{12}H_{20}N_4O_2$ 5g; 25g
Versatile reagent for acids with high pKa's; excess reagent can be readily removed by filtration (after dilution with hexane).[10,11]

Auxiliary Reagents for the Mitsunobu Reaction:

93090 **Triphenylphosphine**, puriss., ≥ 98.5% (GC)
M_w 262.30 [603-35-0] $C_{18}H_{15}P$ 25g; 100g

93092 **Triphenylphosphine**, purum, ≥ 95.0% (GC)
M_w 262.30 [603-35-0] $C_{18}H_{15}P$ 50g; 250g; 1kg

93093 **Triphenylphosphine, polymer-bound**
~3 mmol triphenylphosphine/g resin cross-linked with 2% DVB; particle size 200–400 mesh
– [39319-11-4] Ⓟ-$C_6H_4P(C_6H_5)_2$ 1g; 5g; 25g
An easy and efficient way to completely remove the phosphine oxide at the end of the reaction.

90827 **Tributylphosphine**, pract., ~ 95% (GC)
M_w 202.32 [998-40-3] $C_{12}H_{27}P$ 25mL; 100mL; 500mL
This reactive phosphine gives better results than triphenylphosphine in the Mitsunobu reaction in a number of cases.[12,13]

90540 **Triethyl phosphite**, purum, ≥ 95.0% (GC)
M_w 166.16 [122-52-1] $C_6H_{15}O_3P$ 50mL; 250mL; 1L
Less reactive than triphenylphosphine, but can lead to a more favorable diastereomeric product ratio.[14,15]

(1) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (2) Dodge, J. A. et al. *Org. Synth.* **1996**, *73*, 110. (3) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (4) Mitsunobu, O. *Synthesis* **1981**, *1*. (5) Kiankarimi, M. et al. *Tetrahedron Lett.* **1999**, *40*, 4497. (6) Gennari, C. et al. *J. Am. Chem. Soc.* **1986**, *108*, 6394. (7) Evans, D. A. et al. *ibid.* **1986**, *108*, 6395. (8) Vicario, J. L. et al. *Tetrahedron Lett.* **1999**, *40*, 7123. (9) Carocci, A. et al. *Tetrahedron: Asymmetry* **2000**, *11*, 3619. (10) Tsunoda, T. et al. *Tetrahedron Lett.* **1993**, *34*, 1639. (11) Lai, J.-Y. et al. *ibid.* **1995**, *36*, 5691. (12) Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 5467. (13) Smith, A.B., III et al. *J. Am. Chem. Soc.* **1992**, *114*, 2567. (14) Townsend, C. A.; Nguyen, L.T. *Tetrahedron Lett.* **1982**, *23*, 4859. (15) Bose, A. K. et al. *Can. J. Chem.* **1984**, *62*, 2498.

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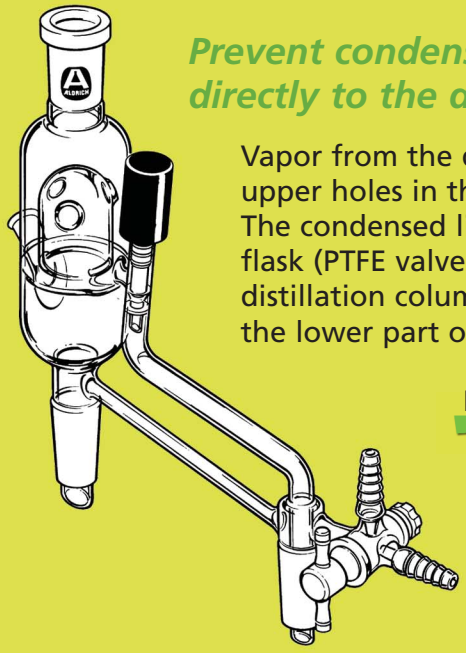


Prevent condensed liquids from returning directly to the distillation column.

Vapor from the distillation column passes through the upper holes in the take-off head and into the condenser. The condensed liquid can be drained into a side storage flask (PTFE valve open, Fig. 1) or allowed to return to the distillation column (PTFE valve closed) through a slot in the lower part of the head.

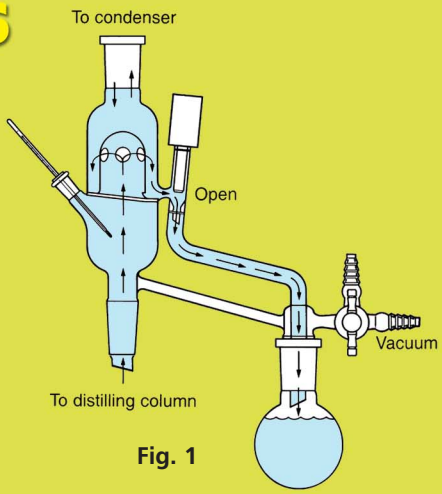


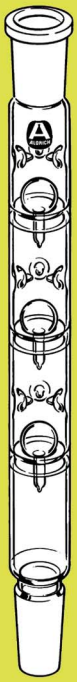
Fig. 1

Features:

- Upper and lower ⅀ joints permit the use of take-off head with different distillation columns and condensers
- Precision PTFE needle valve
- ⅀10/18 thermometer joint
- Vacuum/purge hose connections with PTFE stopcock

⅀ joints	Cat. No.
24/40	Z54,481-7
29/32	Z54,482-5

NEW!

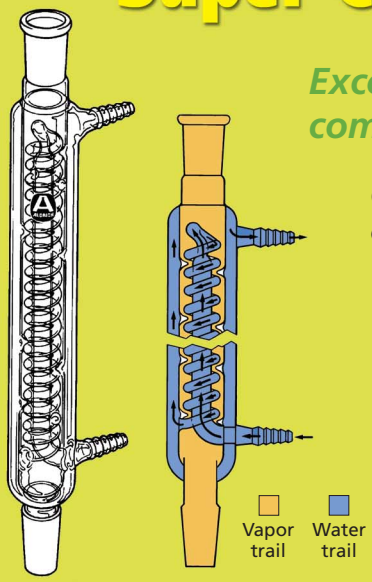


Generation II Snyder Distillation Columns

These improved floating-ball type columns feature robust, solid-glass constrictions for safer handling and integrity. Three sections.

⅀ joints	Cat. No.
14/20	Z54,483-3
24/40	Z54,484-1
29/32	Z54,487-6

Super Condensers



Excellent for volatile compounds.

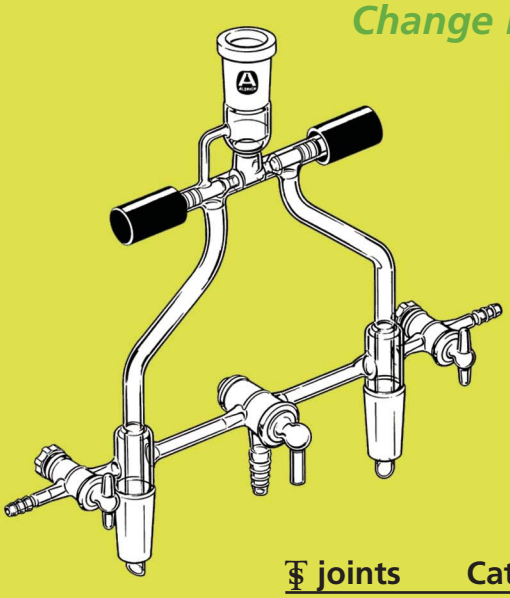
Combine all of these condenser types:

- Cold-finger
- Coiled
- Liebig
- Vigreux

Overall H (cm)	Surface area (cm^2)	⅀*24/40* Cat. No.	⅀*29/32* Cat. No.
32	405	Z22,497-9	Z51,740-2
37	510	Z22,498-7	Z51,741-0
41	610	Z22,499-5	Z51,742-9
51	820	Z22,500-2	Z51,743-7

NEW! Continuous-Receiving-Head Adapters

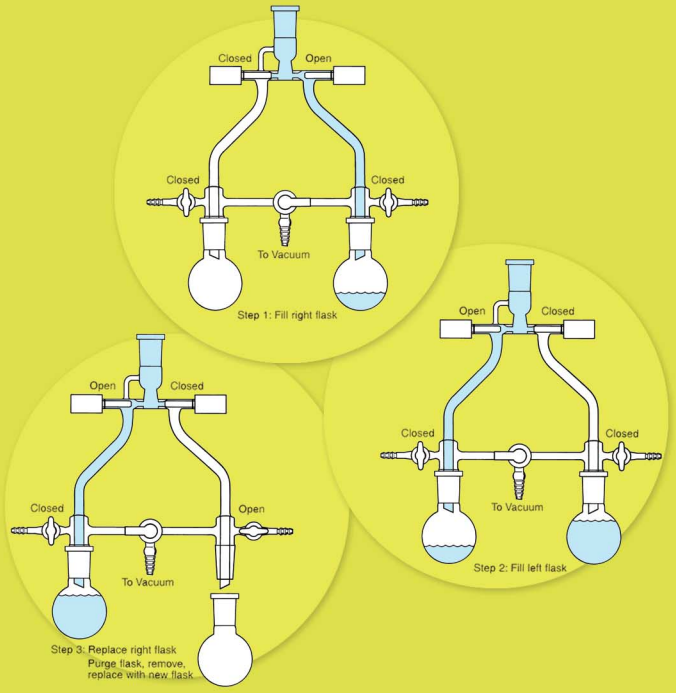
Change receiving flasks without stopping the distillation.



Features:

- Two high-vacuum PTFE needle valves
- One center, two side glass vacuum stopcocks

Ŧ joints	Cat. No.
24/40	Z54,479-5
29/32	Z54,480-9



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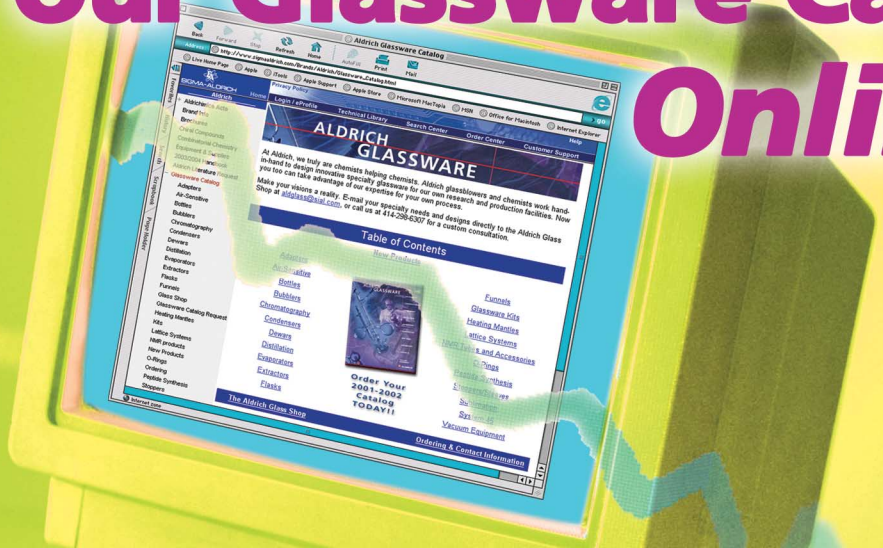

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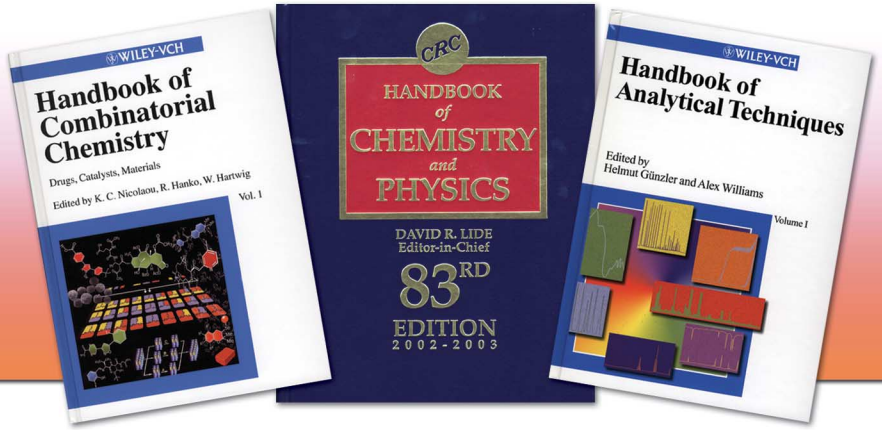

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Ionic Liquids in Synthesis

P. Wasserscheid, Ed., John Wiley & Sons, New York, NY, 2002, 350pp. Hardcover. Ionic liquids not only have the potential to increase chemical reactivity and thus lead to more efficient processes, but also are non-flammable and less toxic than conventional solvents due to their low vapor pressure. This volume brings together the latest developments in this fascinating field and provides numerous practical tips.

Z51,514-0

Ionic Liquids: Industrial Applications for Green Chemistry

R. D. Rogers and K. R. Seddon, Eds., Oxford University Press, New York, NY, 2002, 464pp. Hardcover. One of the first books devoted to room-temperature ionic liquids. A useful guide for chemists interested in environmental protection, synthesis, catalysis, or the modern chemical industry.

Z51,496-9

Green Chemistry: An Introductory Text

M. Lancaster, Royal Society of Chemistry, Cambridge, UK, 2002, 302pp. Softcover. Outlines the basic concepts of the subject in simple language, looking at the role of catalysts and solvents, waste minimization, feedstocks, green-metrics, and the design of safer, more efficient processes. The inclusion of industrially relevant examples throughout demonstrates the importance of green chemistry in many industrial sectors.

Z51,527-2

Laboratory Automation in the Chemical Industries

D. G. Cork and T. Sugawara, Eds., Marcel Dekker, New York, NY, 2002, 384pp. Hardcover. This timely reference explores the broad range of automated techniques being employed by chemists. Written by academics, manufacturers, and practicing chemists in the pharmaceutical and fine chemical industries, the book is divided into two parts covering aspects of automation in chemistry discovery and process development. It features chapters on the design, implementation, and optimization of automated techniques for the production, purification, and analysis of new pharmaceutical and chemical compounds.

Z51,503-5

CRC Handbook of Chemistry and Physics

83rd ed., D. R. Lide, Ed., CRC Press, Boca Raton, FL, 2002, 2,664pp. Hardcover. Provides the widest and most complete coverage of data on properties of inorganic and organic compounds. Includes a new section that marries more contemporary resources, such as the Internet, with existing information.

Z51,474-8

Handbook of Analytical Techniques (2-Vol. Set)

H. Günzler and A. Williams, John Wiley & Sons, New York, NY, 2001, 1,198pp. Hardcover. Serves as a concise, one-stop reference for every professional, researcher, or student using analytical techniques. All relevant spectroscopic, chromatographic, and electrochemical techniques are described, including chemical and biochemical sensors, as well as thermal analysis, bioanalytical, nuclear, and radiochemical techniques. Special articles are devoted to general topics such as chemometrics, sampling, and sample preparation.

Z51,517-5

Handbook of Heterocyclic Chemistry

2nd ed., A. R. Katritzky and A. F. Pozharskii, Elsevier Science, New York, NY, 2000, 748pp. Hardcover. The highly systematic coverage given to the subject makes this one of the most authoritative single-volume accounts of modern heterocyclic chemistry available. Illustrated throughout with thousands of clearly drawn chemical structures. Contains over 1,500 chemical figures and reactions.

Z51,521-3

Handbook of Combinatorial Chemistry: Drugs, Catalysts, Materials (2-Vol. Set)

K. C. Nicolaou, R. Hanko, and W. Hartwig, Eds., John Wiley & Sons, New York, NY, 2002, 1,146pp. Hardcover. This two-volume set deals with synthetic chemistry in all of its forms, ranging from life sciences to materials science. An indispensable reference for synthetic, organic, and medicinal chemists, as well as material scientists.

Z51,483-7

Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis

J. Tsuji, John Wiley & Sons, New York, NY, 2002, 496pp. Softcover. Provides complete coverage of nearly 35 years of transition-metal-complex chemistry. Includes an in-depth treatment of many innovative synthetic methodologies, a classification of all reactions according to substrates and reaction mechanisms, and examples of important applications of transition-metal-catalyzed reactions.

Z51,519-1

The Art of Writing Reasonable Organic Reaction Mechanisms

R. Grossman, Springer Verlag, New York, NY, 1998, 346pp. Hardcover. A classic textbook geared for advanced organic chemistry or special topics courses. The author uses a number of devices to help students understand the material. Also includes extensive problem sets at the end of all the chapters.

Z51,499-3

Chlorosulfonic Acid: A Versatile Reagent

R. J. Cremlyn, Springer Verlag, New York, NY, 2002, 300pp. Hardcover. This book provides a detailed, up-to-date account of the reactions of chlorosulfonic acid with aliphatic, aromatic, and heterocyclic compounds. Reactions with elements and inorganic compounds are also discussed, along with the use of the reagent as a powerful acid catalyst and dehydrating agent. Also reviews the commercial uses and manufacture of chlorosulfonic acid.

Z51,498-5

Pharmaceutical Master Validation Plan: The Ultimate Guide to FDA, GMP, and GLP Compliance

S. I. Haider, CRC Press, Boca Raton, FL, 2001, 208pp. Hardcover + CD-ROM. An essential guide for establishing a master plan in compliance with FDA, GMP, and GLP requirements. Furnishes the building blocks for developing successful validation procedures and enables users to achieve regulatory compliance with time, money, and resource optimization. Provides a concise and easy-to-use reference tool for the testing and validation of pharmaceutical industry products and facilities.

Z51,507-8

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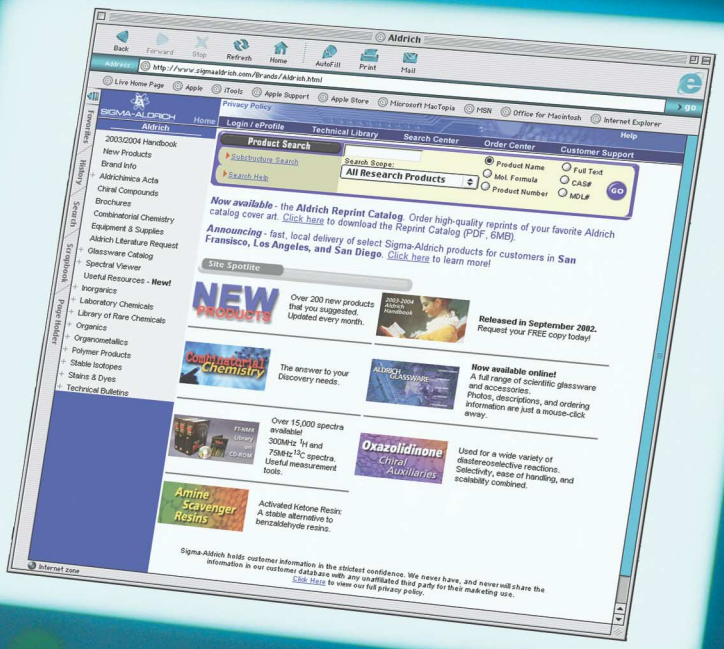

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